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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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CARDIOVASCULAR AND RENAL DRUGS

ADVISORY COMMITTEE

+ + +

86th MEETING

+ + +

Thursday, October 22, 1998

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The Advisory Committee met in the Masur Auditorium, Building 10, National Institutes of Health, Bethesda, Maryland, at 9:00 a.m., Milton Packer, M.D., Chairperson, presiding.

PRESENT:

MILTON PACKER, M.D., Chairperson

ROBERT CALIFF, M.D.

JOHN DiMARCO, M.D.

MARVIN KONSTAM, M.D.

JOANN LINDENFELD, M.D.

PRESENT (Continued):

LEMUEL MOYE, M.D., Ph.D.

ILEANA PINA, M.D.

DAN RODEN, M.D.C.M.

UDHO THADANI, M.D.

JOAN C. SANDAERT, Executive Secretary

CONSULTANTS PRESENT:

LLOYD FISHER, Ph.D.

BARRY MASSIE, M.D.

INVITED GUESTS PRESENT:

JAY COHN, M.D.

DAVID DeMETS, Ph.D.

THOMAS FLEMING

BERTRAM PITT, M.D.

C O N T E N T S

P R O C E E D I N G S

(9:03 a.m.)

CHAIRPERSON PACKER: This is the 86th meeting of the Advisory Committee for the Division of Cardiac and Renal Drugs Products.

Today's topic is to discuss proposed guidelines in the clinical evaluation of drugs for the treatment of heart failure, and before beginning I'll have Joan Standaert review the conflict of interest for today's meeting.

Joan.

MS. STANDAERT: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of this record to preclude even the appearance of such at this meeting.

Since the issues to be discussed by the committee will not have a unique impact on any particular firm or product, but rather may have widespread implications with respect to entire classes of products, in accordance with 18 USC 208, waivers have been granted to each member and consultant

1   participating in the committee meeting.

2   A copy of these waiver statements may be

3   obtained from the agency's Freedom of Information

4   Office, Room 12A30, Parklawn Building.

5   In the event that the discussions involve

6   any other products or firms not already on the agenda

7   for which an FDA participant has a financial interest,

8   the participants are aware of the need to exclude

9   themselves from such involvement, and their exclusion

10   will be noted for the record.

11   With respect to all other participants, we

12   ask in the interest of fairness that they address any

13   current and previous financial involvement with any

14   firm whose products they may wish to comment upon.

15   CHAIRPERSON PACKER: Thank you very much,

16   Joan.

17   We will ask for public comment at this

18   time before we introduce today's meeting. Is there

19   any public comment?

20   (No response.)

21   CHAIRPERSON PACKER: There being no public

22   comment, we really are delighted today to have several

consultants and invited guests to discuss the proposed

guidelines for heart failure, and these include Lloyd

Fisher from the University of Washington; Barry Massie

from the University of California, San Francisco; Jay

Cohn from the University of Minnesota; Dave DeMets

from the University of Wisconsin; Tom Fleming from the

University of Washington; and Bert Pitt from the

University of Michigan.   Bert will be arriving a

little bit later on this morning, as will Dan Roden,

who will be arriving a little bit later this morning,

as well.

The topic for today's discussion of

proposed guidelines for the development of drugs for

the treatment of heart failure, these guidelines have

been in an evolutionary phase for quite some time.

The dates which are on the proposed guidelines which

have been distributed this morning do not represent a

typographical error.

The first time that this committee met to

discuss guidelines for the treatment of heart failure

was, indeed, in December 7th, 1987, and this

represents the second formal open meeting on these

1   guidelines in the last 15 years or so.

2   I had the either pleasure or

3   responsibility of drafting the first version of these

4   guidelines in 1987 and took up the task of revising

5   them for today's meeting. These guidelines for

6   today's meeting have already been discussed at a

7   number of internal meetings in closed sessions and

8   represent the thinking of many, but not necessarily

9   all, of those who are here today.

10   And I want to emphasize that these are

11   draft and these are guidelines. Guidelines do not

12   represent requirements. They represent a sense of

13   what has worked in the past and, perhaps more

14   importantly, what has not worked in the past.

15   Guidelines are obsolete from the day they

16   are issued because the field is too dynamic to be

17   frozen at one point in time, and to draft any document

18   that accurately reflects future development, and I

19   think that needs to be emphasized.

20   This is also a draft guideline in the

21   sense that even this guideline will be wor..ed on after

22   this meeting and will be revised in accordance with

1   many of the suggestions we hear today from all of the

2   members of the committee and all of the consultants

3   and the invited guests, and we would encourage the

4   audience to come to the microphone to participate in

5   this discussion.

6   It is, in fact, intended to be

7   interactive. The only limit to this interaction is

8   really the time available for this meeting. We could

9   go on for days on these guidelines. I'm not certain

10   that would be very fruitful, but the goal really is to

11   have an open discussion and to hear various ways of

12   approaching the development of drugs for the treatment

13   of heart failure.

14   And the hope is that at some point in the

15   future these guidelines may be issued in some formal

16   fashion, although that may take some additional drafts

17   and may take some additional time, and perhaps the

18   next draft of this will have the number 2000 in front

19   of it.

20   Ray, is that possible?

21   DR. LIPICKY: Yes.

22   (Laughter.)

1   CHAIRPERSON PACKER: Okay. The purpose of

2 today's meeting, the structure of today's meeting is

3 to discuss each of the sections of the document in a

4 relatively sequential fashion. The goal is not to

5 read the document. The goal is to really comment on

6 the document.

7   And we've asked specific individuals to

8 lead that discussion, comment on whether the document

9 addresses the needs and the issues, and then to

10 propose specific questions along the way and answer

11 questions along the way that may arise with respect to

12 each of these sections.

13   The first major section that we will be

14 discussing this morning is the section on patient

15 population. That's Section No. 2, and we've asked

16 Joann Lindenfeld to lead off the general discussion on

17 how the document addresses patient population and

18 whether the present way the document is phrased

19 addresses the needs of the field.

20   Joann.

21   DR. MOYE: Milt, can I just ask one

22 question?

1   CHAIRPERSON PACKER: Yes.

2   DR. MOYE: I was telling Ray that I was

3   somewhat panicked on Monday because I hadn't received

4   questions that we usually receive for these sessions.

5   Am I understanding this correctly in that today the

6   committee does not have a formal set of questions to

7   which it should respond?

8   CHAIRPERSON PACKER: That's correct. The

9   reason is because there is, in fact, not necessarily

10   a need to reach answers. The fact is that one can ask

11   any questions one wants, and every member of the

12   committee and all of the consultants can raise issues

13   on any part of the document.

14   So, in fact, the goal here is not to have

15   a finite series of questions and a finite series of

16   answers because it would be very difficult to

17   anticipate all of the questions that could be asked,

18   nor would it be realistic to expect that all of the

19   questions that we could think of could reasonably be

20   answered in the time frame allotted.

21   DR. MOYE: Right.   So if there is more

22   than one defensible answer, is it the purpose of the

1   guideline to encompass that set of answers?

2   CHAIRPERSON PACKER: That's correct.

3   DR. MOYE: And not just one solution?

4   CHAIRPERSON PACKER: Right. So, for

5   example, if a certain dilemma can be reasonably

6   addressed by two or three options, it would be

7   appropriate for each of those options to be listed in

8   the guideline.

9   DR. FISHER: Milt, could I?

10   CHAIRPERSON PACKER: Lloyd.

11   DR. FISHER: I had one thing I thought

12   might be usefully inserted in the introduction, and

13   since we're starting on Point 2 --

14   CHAIRPERSON PACKER: Yes.

15   DR. FISHER: -- and that was I've been

16   involved in a number of discussions where the best

17   study design seems to be something that goes a little

18   bit against what some sponsor has heard from the FDA,

19   and their usual reaction is, "Oh, well, the FDA said

20   they wanted this or are going to do it that way."

21   And I think it would be very useful to

22   have an introduction in the paragraph. This is

implied later when you say science changes, et cetera,

et cetera, but to say the purpose is to get a good

scientific evaluation. If the best scientific

evaluation appears to conflict with these guidelines,

we suggest discussions with the FDA, because it's also

been my experience that when there is really valid

reason for doing something and one talks to the FDA

about it and they see the reason, that they will

either have a very good counter or they will agree.

Granted these are only guidelines and

people shouldn't take them that seriously anyway in

some sense, but nevertheless people will, and I think

it would be useful. In fact, in almost all of the

guidelines that come out, it would be useful to have

something like that.

DR. LIPICKY: Milton, I would second that

from the vantage point that there needs to be emphasis

that we gave in the beginning, that is, that this is

not a proscription of how one should do things. It is

a discussion of things that might be appropriate to

think about.

And there may be ways of solving the

1   problems that aren't even specifically mentioned, and

2   that sets the tone for today also, where I hope the

3   interest is in whether or not the guidelines are

4   written so that they communicate something and that

5   there's some agreement with respect to what they

6   communicate.

7   And so this first issue of make sure that

8   the guidelines are not perceived as a proscription is

9   really fairly important, I think.

10   CHAIRPERSON PACKER: And, in fact, as you

11   will notice, these guidelines rarely -- in fact, if I

12   recall, these guidelines never use the word "must,"

13   and there's been a concerted effort to avoid the word

14   "should."

15   When, in fact, there is a strong feeling

16   about something, that is evident usually by the

17   language of "well, you can do this, but it usually

18   won't work very well." That, I think, reflects the

19   philosophy that both Lloyd and Ray have emphasized,

20   which is if you can find a way of making something

21   that hasn't worked work, it's a good thing to try to

22   bring that forward and discuss it.

1   And frequently, as Lloyd has emphasized,

2   if it's good science, it's usually good drug

3   development.

4   I really want to emphasize, I guess, one

5   thing that Lloyd implied, although I don't think he,

6   you know, specifically stated.   There is a real

7   tendency on those who look at this document to read it

8   literally, and sometimes if the document -- and the

9   document rarely uses very specific language, but where

10 it does, I have heard those who are involved in

11 developing the drugs say, "Well, the document says

12 three months.   So we should do three months even

13 though two months makes more sense."

14   Well, if two months makes more sense, you

15 should do two months and discuss why you're doing two

16 months. That philosophy applies throughout the entire

17 philosophy of the document.

18   DR. THADANI: Milt, a suggestion probably

19 should suffice, the fact that suggestion implies that

20 you can discuss it and everything else right --

21   CHAIRPERSON PACKER: That's right.

22   DR. THADANI: -- in the introduction.

1   CHAIRPERSON PACKER: Okay. We have a lot

2   to cover, and so let's move forward.   The first

3   section is on patient population.

4   Joann.

5   DR. LINDENFELD: Okay.   There are four

6   things that characterize, I think, in this document

7   the patient population, and we'll just go through

8   those individually and bring up a point or two about

9   each: the cause, the severity, concomitant disorders,

10   and concomitant medications.

11   So we'll start with the cause, and these

12   are really relatively straightforward, although not

13   always cause and effect.

14   I think the two issues under cause are

15   whether or not we want to say anything more about

16   ischemic heart disease, and that issue is whether or

17   not ischemic heart disease represents any ischemic

18   heart disease or critical ischemic heart disease that

19   comes up sometimes.

20   In other words, is the patient with an

21   ejection fraction of 25 percent and three 30 percent

22   lesions, coronary disease, or dilated cardiomyopathy?

1   That may not be an issue for this, but that's one

2   question.

3   PARTICIPANT: We can't hear you.

4   DR. LINDENFELD: I'm sorry. Is that

5   better? Okay. Thanks.

6   This is a little short even for me here.

7   The first issue is ischemic heart disease,

8   is whether or not -- if that should be defined more

9   than it is in the document -- that is, whether or not

10   any ischemic heart disease represents ischemic heart

11   disease or dilated cardiomyopathy.

12   That may be more specific than we wish to

13   be in this document.

14   Then I think although not specifically

15   cause, the issue of systolic versus diastolic

16   dysfunction is mentioned, but not precisely defined,

17   and as everyone knows, I think that's a difficult

18   issue, but should we have a precise definition of

19   diastolic dysfunction in terms of ejection fraction or

20   not?

21   Given that that's increasingly part of our

22   heart failure evaluations and a big part of the heart

1   failure population, we haven't specifically addressed

2   that issue in this document.

3   And, Milton, do you want me to just go

4   through each of these areas or stop?

5   That's good.   Thanks.

6   Okay. Under characterization of severity,

7   the document states, "The most reasonable means of

8   grading severity is to quantify symptoms and then to

9   measure fatal and non-fatal events." Of course, the

10   latter is the latter, but the question here is whether

11   or not we wish to say much more about symptom

12   characterization.

13   As everyone is aware, there are several

14   ways to evaluate symptoms and several criteria, and

15   those vary somewhat in definition. We'll just have a

16   brief discussion whether or not we want to be more

17   specific in characterizing symptoms prospectively.

18   These,   I   think,   are   fairly

19   straightforward. The severity of heart failure, there

20   were three classifications of patients that might

21   require study: those who are hospitaliz·d with

22   symptoms at rest, and those symptoms at rest would

include fluid overload resistant to diuretics, acute pulmonary edema, refractory symptoms with poor end organ perfusion requiring IV therapy.

Although these are not defined further, I think the intent would be that those are defined at the time of the study.

Ambulatory patients with symptoms on exertion, and then ambulatory patients with no symptoms or patients who have had symptoms.

In terms of concomitant disorders, this is also generally straightforward, but the document states, I think probably reasonably, that acute heart failure drugs should include patients with acute MI. There could be some discussion about whether or not that's a requirement.

And then something that's not discussed as much, that the study must be used in the population in whom an indication is sought, and I think as we're all aware, very often the population of patients studied with heart failure don't exactly represent the overall population, particularly in terms of age and gender. Whether or not we wish to be more specific about that

1   would be an issue for discussion.

2   And finally, concomitant medications. The

3   document states that patients should be on established

4   therapy for heart failure. The document does not give

5   precise guidelines, and of course, that's a moving

6   target. So that would be difficult.

7   But it also doesn't state what percentage

8   of patients should be on established therapy, not

9   exactly, but large percentage not, and then doesn't

10   discuss international or regional differences, which

11   again is probably not something that needs to be

12   specified, but whether or not we want to discuss a

13   little bit about guidelines for established therapy

14   and how many of the patients should be on established

15   therapy in the study.

16   That's the summary of that section.

17   CHAIRPERSON PACKER: Okay. I'd like to

18   open up a discussion on all of the topics that Joann

19   has covered.

20   Let me first state that the types of

21   patients evaluated in a clinical development program

22   do not necessarily relate to whether the formulation

1   is intravenous or oral and do not necessarily relate

2   to whether the uses proposed there are for short term

3   or long term administration.

4   The patient population, although it might

5   be reasonable to think that an IV drug is most likely

6   to be used in hospitalized patients with symptoms at

7   rest and an oral drug is more likely to be used in

8   ambulatory patients with symptoms on exertion, the

9   fact is that we are all aware that there are

10   differences. That's not always true. IV drugs can be

11   used in ambulatory patients with symptoms on exertion,

12   and oral drugs can be used in hospitalized patients

13   with symptoms at rest.

14   So these classes, these three classes of

15   patients, are not intended to replace the traditional

16   classification of acute versus chronic or IV versus

17   oral.   They are intended to define a patient

18   population that is the target population for clinical

19   use.

20   And despite the fact that we can make that

21   classification very, very complicated, and in the past

22   there have been separate ways that have been proposed

1   to evaluate mild to moderate heart failure from severe

2   heart failure, it's very difficult to distinguish

3   moderate and severe heart failure. It's a continuum.

4   But it's relatively easy to identify these

5   three groups of patients. So let me emphasize that

6   the grouping of patients, the identification of

7   patients to be studied is an important characteristic

8   of drug development which is related to, but not the

9   same as the decision as to whether one develops an

10 oral or IV drug for short or long term use.

11 Comments from any member of the committee

12 on this section of the document?

13 DR. THADANI: If I may start, one of the

14 difficulties sometimes is to be absolutely sure

15 whether the patient has coronary disease or not. All

16 of us see patients who might have Q waves on the ECG,

17 and yet you do a coronary angiogram, and you don't

18 have CAD.

19 So I think short of doing angiograms on

20 everybody, which sometimes, you know, you don't want

21 to do it if EF is ten percent just to quantify the

22 severity of CAD because the patient may not be

1   operable, so you would argue why bother doing it.

2   How much does it really make a difference

3   to outcome? That's one concern.

4   Another concern is if a patient has

5   cardiomyopathy, say, idiopathic or wild, and then you

6   do a coronary angiogram and they have 30 percent

7   lesions, and yet they could be prone to death because

8   of rupture. So it becomes a concomitant condition.

9   So I'd like some comments from Joann or

10   yourself how you tackle that.

11   CHAIRPERSON PACKER: Well, let's try to

12   ask Joann since she was the discussant for this.

13   Joann, the document is fairly silent on

14   the vigor with which one needs to pursue the --

15   whether the exact diagnosis. It simply says that the

16   diagnoses need to be characterized.

17   How important is it? Do the sponsors need

18   to, if someone says that they have coronary disease,

19   need to define that any further, or is the clinical

20   judgment of the investigator sufficient?

21   DR. LINDENFELD: I think that the clinical

22   judgment of the investigator, along with the usual

1   guidelines we've used, the presence of angina or Q

2   waves on EKG, things like that, are probably enough

3   for characterization.

4   CHAIRPERSON PACKER: Rob.

5   DR. CALIFF: Milton, I might comment that,

6   you know, I would regard this as a classic example

7   where the answer is "it depends"; that in general, if

8   the goal of a therapeutic program is to develop a

9   therapy for heart failure, in general, I would agree

10   completely with Joann.

11   If someone developed a drug, let's say,

12   that they thought really only worked in patients with

13   ischemic heart disease or without ischemic heart

14   disease, then a rational program would have a Phase 2

15   where everyone would have an angiogram, and maybe

16   Phase 3 in an attempt to find out what would happen if

17   the treatment was really used in practice, would

18   emphasize careful evaluation clinically, but would not

19   require an angiogram.

20   CHAIRPERSON PACKER: Yeah, Marv.

21   DR. KONSTAM: I basically agre with Rob.

22   I think, you know, we've seen places where based on

1   various studies the conclusion might be drawn that the

2   drug works in ischemic heart disease and not in

3   nonischemic or vice versa, and I think that if you

4   wind up with that conclusion, but are left, when you

5   go back and look at the study, with all it was was a

6   check box of the investigator saying, "I think this is

7   ischemic heart disease," then you're left with

8   labeling that says, you know, this drug works if the

9   clinician thinks it's ischemic heart disease, and I

10   don't think that's very helpful.

11   So I think if you're going to wind up

12   seeking an indication for, you know, a particular

13   subcategory, then I think you're going to have to work

14   a little harder to define that and what the criteria

15   are for establishing that etiology.

16   DR. THADANI: I think it becomes very

17   relevant even in some of the studies in which you are

18   the principal author. You know, there's a subgroup

19   analysis of ischemic versus nonischemic, and yet I'll

20   give you an example of a patient recently. She has

21   rormal coronary arteries, and she keeps on having

22   chest pain, which really sounds like an unstable

1   angina pattern, and yet repeat angiogram still is

2   normal.

3   So I think those are major dilemmas. So

4   if you're saying for ischemic heart disease that you

5   really should either have a documented MI by either

6   ECG or enzymes or both and a coronary angiograph to

7   label it; otherwise I think if you don't have a

8   coronary angiogram or Q waves, even when a patient has

9   history of chest pain, probably the unknown etiology

10   might be the best way to label it.

11   The other issue, I think, perhaps that

12   would be very relevant before you even define the

13   cause of heart failure. I think the front statement

14   should say one should know whether the patient has

15   systolic or diastolic dysfunction because all of the

16   trials are requiring basically ejection fraction one

17   way or another.

18   So I think it's up front that you're

19   dealing either with systolic or diastolic dysfunction

20   because most of the things you're talking in therapy

21   are all really so far related to systolic dysfunction.

22   There's little knowledge on the management of

1 diastolic dysfunction, at least from my reading, at

2 the present time.

3   So I think it should come right in the

4 front and then go to the causes.

5   CHAIRPERSON PACKER: Udho, let me take

6 that last comment and generalize it into a question to

7 the committee and to the consultants.

8   Section 2.3 makes some very specific

9 statements about the kind of experience which would be

10 desirable in an evaluation of a drug, and although it

11 says the section is concomitant disorders in

12 medication, it, in fact, comprises the question, Udho,

13 that you just mentioned.

14   The statement says, "It is clear that the

15 drug development program should define efficacy and

16 safety of a new drug in the patient population in whom

17 an indication is being south. However, the sponsor

18 should also define the efficacy and safety in any

19 patients who are likely to receive the drug if it were

20 approved, even though the sponsor is not seeking a

21 claim for such patients."

22   Now, the rest of the paragraph gives a few

examples of this, but the intent of the wording here

is to make clear that a drug development program is

not only clinical relevant, but sufficiently

comprehensive that if a drug were commercially

available, the patients who are likely to receive it

as a minimum would be able to receive it safely.

Now, two of the examples that are given

here -- and these are not intended to be the only

examples -- it would be perhaps a little bit

inappropriate or inadequate for a drug being proposed

for short term IV use to exclude patients with an

acute myocardial infarction since such a substantial

number of people might be candidates for short term IV

use, have an acute myocardial infarction, and the

safety of the drug in a patient with acute MI might be

different than a patient who has stable or chronic

heart failure that is acutely decompensated.

It would in a parallel fashion perhaps be

inappropriate for a sponsor to define a patient

population in chronic heart failure, all of whom are

get⁺ing, say, -- everyone in the clinical development

program was not on a conventional therapy, was not

even on any commonly used product that was considered

to be very important in treatment of heart failure,

and yet it's very likely that that drug would be used

in patients with that background therapy, like an ACE

inhibitor.

Now, the intent here is not to make this

prohibitively comprehensive, but to simply state that

the drug development program has to be sensitive to

not only the indication being sought, but the

potential for how the drug would be used in the

community.

So my first question to all of the

consultants is: is this appropriate?

The second question that I have to the

committee and consultants is a common example of this

phenomenon is the fact that patients with heart

failure, as Udho has emphasized, in clinical trials

commonly have an ejection fraction criteria, and only

patients with an ejection fraction less than a certain

arbitrary amount are included, therefore, including

only patients with systolic dysfunction.

Yet when drugs are released in the

1   community, patients who have heart failure associated

2   with preserved systolic function may get the drug, in

3   fact, are likely to get the drug because I'm not

4   certain how often ejection fraction is measured in

5   clinical practice.

6   Is there any obligation on the part of a

7   sponsor to at least define the safety of a drug being

8   proposed for systolic dysfunction in patients with

9   diastolic dysfunction? And if the answer to that is

10   yes, how would one do that?

11   Well, we'll go all the way around, and

12   let's say Marv, Lloyd, Barry, Jay, Ileana, and then

13   Bob.

14   DR. KONSTAM: First I just want to make a

15   point. I'd like to propose that we abandon the term

16   "systolic dysfunction" and "diastolic dysfunction" and

17   just substitute for it what we're talking about, which

18   is high -- normal ejection fraction or low ejection

19   fraction.

20   Okay? Does everybody agree with that?

21   DR. THADANI: It's really not true because

22   I agree with you in principle. Yet the trials have

1   arbitrarily cut out the EF either at 40 or 35.   I

2   don't think there's any trial data in patients with

3   heart failure due to either severe systolic

4   dysfunction or mild in which the drugs that we're

5   talking about, life saving, have been shown with the

6   exception of acute MIs.

7   DR. KONSTAM: I'm just talking about

8   terminology, just terminology.

9   DR. THADANI: If you change that, I think

10   you run into the trouble that Milt is say.   Unless

11   your trial is open to all comers, you still need

12   the -- how are you going to define normal?   Is it 60

13   or 50?

14   DR. KONSTAM: However you're going to

15   define it, I'm just talking about terminology.   I

16   would rather say something about ejection fraction

17   since that's what we're measuring rather than saying

18   diastolic dysfunction because, in fact, people with

19   heart failure probably all have diastolic dysfunction

20   even if their ejection fractions are low.

21   It's just terminology, is really all I'm

22   talking about.

1   Okay. I guess I would say I have a

2   problem with, you know, the wording here and the

3   concept that you're saying, Milton. I think in

4   practice it's going to be very difficult to achieve

5   what we're asking, and I think leaving it relatively

6   vague is going to wind up not accomplishing very much.

7   And so what I mean, for example, is that

8   in point of fact, historically and, I think, into the

9   future drugs evaluated for acute hemodynamic

10   intervention, as an example, are typically going to

11   begin and maybe end with excluding patients with acute

12   myocardial infarction from the study group.

13   Now, I think then what are you left with?

14   I think that I sympathize with the view that, you

15   know, some clinicians are going to start using it in

16   patients with MI, but I would say, first of all, that

17   it's fairly onerous for the sponsors to anticipate all

18   of that and to anticipate, for example, that, well,

19   people are going to use it regardless of what the

20   ejection fraction is or they're going to use it in

21   patients with acute MI.

22   I think once you start going with that, I

1   don't know where you end in terms of the obligation of

2   the sponsor to guess at what clinicians are going to

3   do.

4   And then beyond that, I think even if you

5   do guess, I'm not sure what you accomplish. I think

6   if you develop a drug for acute therapy in stable or

7   with exacerbation of heart failure in the absence of

8   acute MI and then you say, "Well, I'm going to study

9   some MI patients in the process," I don't know what

10   you accomplish unless you go out and say, "Well, guess

11   what. I'm going to study this in acute MIs and have

12   a complete development program where you investigate

13   the safety and efficacy of the drug in patients with

14   acute MI."

15   Short of that, if you just have some MI

16   patients in your population, I think you wind up not

17   having accomplished the goal anyway. So my own view

18   is to back off of this.

19   CHAIRPERSON PACKER: Yeah, Marv. I want

20   to underscore the points that you've just made as we

21   go around the room because I think many will echo the

22   same points.

1   But as we go around the room, let me just

2   lead off a question here.   Is there any reasonable

3   guidance that can be provided here at all?   And the

4   reason I'm asking it is that I have a feeling that

5   there are some examples that the committee would

6   generally feel in the future is likely to be

7   sufficiently important that they might even reject a

8   drug for a specific indication because a certain

9   patient population wasn't studied.

10   In other words, the lack of data in acute

11 MI or the lack of data on concomitant meds. or lack of

12 data in diastolic -- I'm sorry -- preserved ejection

13 fraction -- forgive me -- is this ever -- is this

14 always going to be something that can be handled in

15 labeling, that is to say these data are missing, or

16 would the omission of such data ever be of sufficient

17 concern that one could even say this is a silly

18 application?   It studies no one in clinical practice

19 whom a physician will ever see.

20   In other words, is there a reason -- we

21 could take this out complete, but the question that

22 arises is: is there an example where the principle is

1   sufficiently important that you would want to send a

2   signal that it's a principle that's important,

3   although the execution of the principle may be

4   difficult to carry through?

5   DR. KONSTAM: Well, I think there is an

6   example that I recall. We looked at a drug that was

7   a vasodilator for treatment of acute hypertension, if

8   I remember correctly, and the point came out in the

9   discussion that there was no investigation of the

10   safety of the agent with concomitant beta blocker use,

11   and it was anticipated that, in fact, since the drug

12   causes reflex tachycardia, it would be very common to

13   use beta blockers, and we're going to be in big

14   trouble.

15   Now, there was an example, I think, where

16   the panel said, you know, there isn't actually going

17   to be a population in reality where you've proven that

18   the drug is safe and effective because the vast

19   majority are going to be receiving a drug that you

20   haven't looked at.

21   I think that that might be the general

22   point, that when the FDA or the advisory panel

1   encounters something like that, it's going to be very

2   negative about approving the drug.

3   I think that's different from anticipating

4   sort of a clinician creep in the application of the

5   agent, such as saying that you're going to approve a

6   drug in exacerbation of heart failure, but that's

7   going to creep into the acute MI setting.

8   I think maybe that's the difference

9   between the two circumstances.

10   CHAIRPERSON PACKER: I am not certain I

11   actually understand the difference between one and two

12   because one could easily imagine, for example, if

13   someone did a clinical study in patients all of whom

14   were under the age of 60, just another example of the

15   kinds of things that one -- I mean, it may be an

16   absurd example, but maybe not necessarily, but really

17   with the recognition that two thirds of patients with

18   heart failure are over 60.

19   Now, that might be an example in your

20   second category that's totally unacceptable, but one

21   cou¹d imagine all sorts of examples in which the

22   distinction between your first and second example

1   isn't all that clear cut.

2   DR. KONSTAM: I agree. It's not absolute.

3   CHAIRPERSON PACKER: Okay. We'll try to

4   take the original order. I just wanted to get this

5   concept in play because there aren't too many

6   controversial aspects of Section 2, but this is worthy

7   of discussion.

8   Lloyd.

9   DR. FISHER: Yeah, this concept, of

10   course, also appears multiple places throughout the

11   document, and I had some troubles with it both

12   philosophically, ethically, and practically.

13   We've always expected some additional

14   data, for example, organ dysfunction if the organ

15   relates to metabolism or elimination, experience with

16   concomitant therapies that will occur, and so on.

17   In safety you talk about open label

18   extensions as not being much use because they're in

19   control, which makes me think that you have in mind

20   controlled collection of data in these people. Is

21   that correct or incorrect, or is that open to

22   discussion?

1   If it's controlled, then you're

2 essentially beginning to go for the indication. My

3 assumption actually is if this is done, it will be

4 uncontrolled, and then you have tremendous

5 interpretation problems.

6   You're probably moving into higher risked

7 populations so that if you pull all of the adverse

8 event data, you're going to get a misleading profile

9 for the clinician actually. So then the natural thing

10 to do is to break the adverse event profile out into

11 those who are in the indication that you have for the

12 drug and those that you have for these other classes,

13 and I wonder if this doesn't implicitly begin to apply

14 FDA maybe not approval, but certainly acceptance of

15 the fact that it will be used widely.

16   And to me there's a philosophical issue

17 here about how the FDA wants to go about this, as to

18 whether this does imply that, yes, we know you're

19 going to use it here. We don't have the data. Better

20 to give you a little safety data for this indication

21 where comparative safety and efficacy is not

22 evaluated, and I have questions as to whether that's

1   a good thing to do to that extent.

2   CHAIRPERSON PACKER: Lloyd, the one thing

3   which is commonplace in labeling that we see all the

4   time is a paragraph in labeling that goes something

5   like this. "This drug has been used safely in

6   combination with the following 117 medications," and

7   the whole list follows, even though the exposure in

8   each one of those examples could have been a very

9   limited number of patients, and it's almost always

10   uncontrolled.

11   So it's difficult. This is a general

12   principle not only for heart failure development, but

13   for drug development in general.

14   Barry.

15   DR. MASSIE: Yeah. I tend to agree with

16   a lot of what's been said, particularly a lot of what

17   Lloyd just said.

18   I mean, it is confusing. I don't think

19   that we can answer these questions, but I have, I

20   think, as you do, a lingering concern particularly

21   with the acute MI setting, which is where a large

22   proportion of the use of many drugs that we approve

1   for acute exacerbations of heart failure are used.

2   But then we hit the enigma that Lloyd just

3   brought up. Do we insist on a controlled study in

4   that group or do we just insist on some experience,

5   that if it was awful enough would point attention, but

6   otherwise we'll not know how to assess it without a

7   control group?

8   And I really don't have an answer for

9   that, but I think that as you talk in the later

10   documents or later in the document you talk about

11   numbers of patients exposed. It would seem to me that

12   those numbers have inflated compared to the packages

13   that we've seen in the past, particularly in the acute

14   heart failure arena, and that does leave room for a

15   substantial number of patients exposed to open label

16   therapy in some of these areas.

17   Difficult as it may be to evaluate that

18   data, I think we learn some important things, and so

19   I would say the way you'd handle that acute MI problem

20   would be to say, yes, you know it's going to be used

21   in acute MI. We know it's going to be us d in acute

22   MI. Get some exposure in acute MI as part of your

1   1,500 patients you need.

2   One other point I wanted to make that gets

3   back to the preserved systolic function. I think that

4   that's going to have to be labeling because you can't

5   really force people to study an entity they don't

6   think is going to work just because somebody might use

7   it, say digoxin as a prime example of where you

8   wouldn't want to probably do a study with high EFs.

9   Do you have to? I don't think so, but we

10   haven't done such a good job in labeling these drugs

11   to make that clear. You know, some of these approvals

12   for chronic heart failure have left out the ejection

13   fraction in the indication.

14   So I think that's where we ought to handle

15   that aspect. Make it clear up front who has been

16   studied and who it's indicated for and not assume it's

17   all heart failure.

18   CHAIRPERSON PACKER: Yeah. Well, let me

19   pause for a second and ask both Ray and Bob. The

20   trend these days has been to describe the indication

21   of a drug for heart failure as for heart failure, and

22   depending on if it's short term or IV or oral, but

with only one exception I can think of, the indication

does not mention the ejection fraction. Actually two

indications that I can think of the drug does not

mention, the indication section does not mention the

ventricular function.

The exceptions that I can think of is the

use of analopril in asymptomatic patients with LV

dysfunction. It actually says that, and in the

carvatelol labeling it says in patients with an

ischemic or nonischemic cardiomyopathy, the

implication being systolic dysfunction, but everything

else is labeled for heart failure even though all of

the data are in patients with low ejection fractions.

Is there a desire to make that more

specific in future drug development?

Ray.

DR. LIPICKY: Well, I think you get two

answers: not on my part. Now it's up to Dr. Temple.

CHAIRPERSON PACKER: Bob?

DR. TEMPLE: I think the discussion has

been mixing multiple concepts. Let me say what I

mean.

1   We have a general recent, ten-year, say,

2   encouragement of sponsors to include a wide range of

3   patients in their trials, that is, not to exclude

4   people over 65 reflexly, not to exclude concomitant

5   therapy, not to leave out diabetics, et cetera.

6   The expectation though is not that you're

7   going to do separate studies in each of those

8   subpopulations. It's that there's going to be enough

9   of them so that you can look across your studies and

10   make some reasonable assessment of whether there's a

11   big difference between one group and another.

12   Of course, you can't randomize to that

13   characteristic. So you're somewhat limited.

14   You're partly discussing that, and you're

15   also partly discussing specific subsets of heart

16   failure patients who might really be expected to

17   respond differently and who may or may not deserve

18   specific attention.

19   You wouldn't carry out a trial in heart

20   failure and just include a small number of people with

21   acute MIs. You'd pull them out and do a separate

22   study, I think. I can't imagine why you'd take the

1   risk of mixing them and confusing the situation.

2   So I think this guidance document should

3   reach a conclusion about whether a drug for heart

4   failure really ought to be studied in people with

5   acute MI or at least whether that ought to be

6   considered, and the sponsor should explain why the

7   sponsor decided not to or to as a separate condition.

8   Similarly, the guidance document ought to

9   address the question of whether people with normal

10   ejection fraction heart failure ought to be a study

11   population that is examined, and as Barry just said,

12   you might reach a different conclusion for an

13   ionotrope and for a vasodilator.

14   So I think that's up for discussion. My

15   own view is that, as everybody has learned that heart

16   failure needs to be thought of in at least two

17   classifications, the reason to distinguish the two

18   groups and study both at least a little becomes

19   reasonable.

20   But, for example, if you didn't expect

21   much in high ejection fraction patients, it might be

22   that a short term clinical pharmacology type study

1   measuring cardiac output or other things might be

2   enough to say there's no point in proceeding further.

3   I mean, you know, you have to think about

4   that and tell us whether you think that's right. You

5   wouldn't necessarily have to do a full bore

6   development program on something that isn't very

7   probable, but I would argue that the major categories

8   probably ought to be discussed. That seems to me one

9   of the things the guidelines should address.

10   But it's very important, I think, to

11   distinguish between specific groups that ought to be

12   studied in a formal and rigorous way and just a more

13   general urging to don't exclude people, and if you

14   don't exclude people, you'll get plenty of diabetics

15   and plenty of hypertensives and plenty of all those

16   things, and you can look at the subsets and see if

17   there's anything grossly stunning.

18   CHAIRPERSON PACKER: Bob, just a specific

19   question. Is there -- I guess Ray has answered this

20   in the negative. The question is whether you'd feel

21   differently. Would future labeling for drug be if

22   only patients with low ejection fractions were studied

1   -- reflect the fact that the indication is only for

2   patients with low ejection fractions as opposed to for

3   heart failure?

4   DR. TEMPLE: No, I think it should make

5   that distinction. I think, in fact, virtually all

6   trials have included mostly low ejection fraction

7   patients, but I don't actually know that, and I'm not

8   sure it was always looked at.

9   But I would think if the drug is not

10   likely to be or known not to be useful in one subset,

11   that seems quite reasonable.

12   One of the things that I would think would

13   be troublesome would be too much stress on the

14   etiology of the disease because it seems to me it's

15   more the functionality of the disease that's

16   important, not how you got there. That's another

17   question.

18   DR. LIPICKY: But from what we have seen

19   in results, the etiology of the disease seems to

20   predict outcome variables as a function of treatment

21   more accurately than whether there's preserved

22   ventricular function or not preserved ventricular

1   function.

2   DR. TEMPLE: Is that so?

3   CHAIRPERSON PACKER: How's that?

4   DR. TEMPLE: Is that so?

5   DR. LIPICKY: In ischemic and nonischemic

6   heart disease, does that not --

7   DR. TEMPLE: Not really. I don't know of

8   any analysis that showed that.

9   DR. LIPICKY: With good ejection faction

10   and poor ejection faction?

11   DR. MASSIE: Well, you can't comment on

12   the good or poor because there's no data on poor. So

13   you can't say that anything has been better or worse

14   than that discrimination because we only have one side

15   of the coin there.

16   And I guess what we used to think is the

17   discrimination   between   ischemic   and   nonischemic

18   doesn't seem to be panning out as much as it used to

19   be when we had beta blockers that only had positive

20   trials in nonischemic types of patients. That was, I

21   think, the biggest group that we've ever studied where

22   there seemed to be that discordance.

1   CHAIRPERSON PACKER: But that discordance

2   has disappeared.

3   Jay.

4   DR. TEMPLE: One last comment. Etiology

5   obviously could make a huge difference to such things

6   as survival. So you would be crazy if you didn't try

7   to balance those things in a large outcome trial.

8   But whether symptoms of heart failure get

9   better may or may not be related to etiology.   It

10   seems a little unlikely that it would relate to

11   etiology as opposed to a functional measure.

12   CHAIRPERSON PACKER: Jay and then Bert.

13   DR. COHN: No, I think the problem that

14   we're going to be in here throughout the day is the

15   distinction of the disease as a symptom disease in

16   which there are three classes of patients based upon

17   symptoms, and now our concern is how do you control

18   physicians using drugs to treat symptoms when, in

19   fact, all of the drugs that we develop to treat so-

20   called heart failure really are aimed at specific

21   mechanisms of the disease.

22   And it seems to me imprudent to demand

that a mechanistic or a drug with a known mechanism be studied in patients who do not have that mechanism to treat. If you had a diuretic and you were using that to treat heart failure, would you need to study it in patients who do not have congestion to show that it is safe, or would you demand that the drug be marketed for treatment of congestion in heart failure? And that allows you to use it in a targeted population.

If you had a drug which lowered LDL and you decided you wanted to demonstrate that patients who had an elevated LDL and coronary disease if taking this drug will have a reduced incidence of morbid events and mortality in heart failure, would you need to study that drug in patients who do not have an elevated LDL and who do not have coronary disease?

I think you would all agree it would be foolish to do that because that's not the patient targeted population.

So it seems to me the same thing could be said about ventricular dysfunction. If you have a drug whose target is to reduce the remodeling process in the left ventricle and make the chamber smaller, it

would be imprudent to use that drug in patients who do

not have a dilated ventricle and a low ejection

fraction.

Now, would we have to study that drug in

that population with a normal ejection fraction

because some physician in practice will use this drug

to treat heart failure with a normal ejection

fraction?

I would say no. I think the labeling

could reflect exactly the indication for the therapy,

and it would not be indicated for heart failure. It

would be indicated for a dilated ventricle with

symptoms of heart failure.

Now, maybe that's asking the practicing

community to be more sophisticated, but it seems to me

that's the direction we should be going in, and this

document as it's written tends to exclude thoughtful

mechanistic insight into the disease that we're trying

to treat, and I don't think we should discourage that

process within the FDA or in the practice community,

and we should probably try to move the ₁ractice

community more toward understanding the sites of

1   action of the drugs that they're using in this very

2   complicated syndrome.

3   The more we talk about heart failure and

4   try to find a treatment for heart failure, the more

5   trouble we're going to get into because it is a very

6   heterogeneous syndrome, and the drugs that we use are

7   very diverse in their sites of action.

8   CHAIRPERSON PACKER: Jay, just the way to

9   get from A to B is, in act, to recommend to the agency

10   that their indications be made more specific and that

11   their specific mention of patients who have not been

12   studied be noted specifically.

13   DR. COHN: Absolutely.

14   CHAIRPERSON PACKER: And so that the best

15   way to deal with this dilemma is to provide

16   appropriate direction to physicians as to who was

17   studied, who it was effective in, who was not studied,

18   and so the burden now falls on the physician as

19   opposed to the pharmaceutical manufacturer.

20   But that could only happen if Ray's

21   answers to the question that we posed to me were that

22   he would contemplate making it more specific because

1   right now it's been pretty general.

2   DR. LIPICKY: But I guess convince me some

3   more. In practice, there are two ways of going about

4   it. One is you take the inclusion/exclusion criteria

5   written in the protocols, which generally are bias and

6   prejudice that comes from investigators and the

7   companies who are developing things, which may or may

8   not be entirely consistent with my model of what is

9   important in heart failure, but that is how the

10   patients were selected so that you're being entirely

11   empirical, which would then probably also make me need

12   to account for the color of hair, the color of eyes,

13   racial, you know, ethnic background.

14   I don't know that none of those things are

15   important. So then that's what labeling would be or,

16   alternatively, you accept somebody's model for what is

17   important in heart failure and to then abstract from

18   on that model dependent basis those things that were

19   in the inclusion/exclusion criteria that I know are

20   important and to include those in the indications.

21   So I guess I gave a negative answer

22   because I would not be uncomfortable with the notion

1   that a doctor says this patient has heart failure, and

2   I'm going to test drug versus placebo, and you draw

3   conclusions, and then the indication is heart failure,

4   and that most of the notions about etiologically

5   specific outcomes as a function of therapy, in fact,

6   come from subgroup analyses, and when you get a large

7   enough bunch of data together, it turns out most of

8   those suspicions turn out not to be right.

9   So that I would argue against having the

10   ability to do subgroup analyses because they usually

11   confuse rather than straighten out. So I think I need

12   some convincing that I know enough to be able to say,

13   yeah, I only know this works in people with low

14   ejection fraction, and that I would know for sure that

15   people with normal ejection fraction would not be

16   positively affected or might be adversely affected.

17   I have not seen data of that nature, but

18   maybe   someone   knows   that   that's   already   well

19   demonstrated.

20   CHAIRPERSON PACKER: Bob.

21   DR. TEMPLE: I think one of the goals of

22   this   guideline   should   be   to   identify   those

1   characteristics that Ray hasn't seen yet that define

2   populations that ought to be studied separately or

3   considered as potential separable populations.

4   For example, if it's not reasonable in the

5   view of the people working on the guideline to think

6   that people with low ejection fractions and people

7   with high ejection fractions would respond the same

8   way to an ionotrope, then at least when you're

9   studying an ionotrope it becomes important to

10 distinguish the populations.

11   I can imagine labeling that would say this

12 drug was not studied in people with normal ejection

13 fraction because there was no reason to think it would

14 work in those people. You might do that.

15   But as I hear this, there are several

16 categories of people who might be distinguished. For

17 example, everyone seems to think that people with an

18 acute MI are a separate enough group that they ought

19 to be looked at. As Jay pointed --

20   DR. CALIFF: No, not everyone.

21   DR. TEMPLE: You just throw them in the

22 regular study?

1   DR. CALIFF: Well, I --

2   DR. TEMPLE: Well, okay. That strikes me

3   as incautious and a bad idea, but, you know, we can

4   talk about it.

5   But whether or not you would put them in

6   the same study or not, enough people think they're a

7   different group that you ought to think about them.

8   Similarly, high and low ejection fraction

9   might be very important for some categories of drugs.

10   Maybe it's not so important for a vasodilator.   I

11   don't know, but those are the sorts of questions that

12   I would think should be addressed.

13   If there were other important categories

14   that deserve special thought or a special look,

15   whether that's resolved by specific studies or by

16   labeling is not the most important question.   This

17   document should identify those.

18   DR. COHN: I guess the question though is

19   whether one could gain approval of a drug studied in

20   a very targeted population that is clearly definable,

21   but is not generalizable, and if the labeling could so

22   indicate that the drug is clearly effective in that

targeted population and hasn't been studied in a wider

population. Is that an approvable drug or not?

DR. TEMPLE: Potentially, but there are

two questions that have to be asked.

We've been burned, we think, lately by

attempts to restrict drugs to particular populations

because people don't follow the advice. Where there's

a safety concern associated with that, we might well

argue -- it would depend on how wonderful the drug

was, of course -- we might well argue that more

information is needed before approval, but in other

circumstances we might say we'll let labeling try to

do this, but --

DR. LIPICKY: It   is   potentially

approvable.

DR. TEMPLE: Yeah, it is. It sort of

depends on what it is, but we're increasingly

skeptical about the ability of labeling to direct

therapy. So if there's a real safety concern about

something   because   it   wasn't   studied   in   a

subpopulation, we might be worried about that.

DR. COHN: Well, I guess that that then

falls on the role of the FDA in terms of the practice

community because if, indeed, you need to demonstrate

safety in a large population of patients who don't

fall into the category where the drug would be used --

a patient with a normal LDL in whom you don't want to

study an LDL lowering drug -- do you have to show that

it's safe in that population because physicians are

liable not to measure LDL and, therefore, use the

drug, or can you accept the restricted labeling that

this drug hasn't been studied in people with normal

LDL?

DR. TEMPLE: There is no single answer,

Jay, but take the acute MI situation. I think you

have a much better case for arguing in that setting

that there ought to be some experience if you think

it's likely the drug is going to be used there.

DR. COHN: Well, I think that raises the

issue about ischemia and the safety, and this is a

patient population that has a high incidence of

ischemia. You'd like to know that the drug is safe in

·schemia. So I think --

DR. TEMPLE: I think each case is

1   different. They're not going to all fit in the same

2   box.

3   CHAIRPERSON PACKER: Rob?

4   DR. CALIFF: I want to comment on two

5   issues, both of which have been raised, and the first

6   is I would like to take the radical position for the

7   sake of discussion on a myocardial infarction.

8   You know, as a CCU director for a long

9   time and for some reason having a spate of relatives

10   with acute heart failure recently and talking to

11   doctors trying to figure out what in the heck to do

12   with these people, I think we've got a real problem.

13   This is the national public health

14   epidemic, is acute heart failure, and it's true that

15   if you follow patients in a heart failure clinic and

16   look at your population admitted, it's a somewhat

17   discrete population, but if you take the inception

18   point as the emergency department or the CCU, which is

19   where the decisions are really made, you do not know

20   in the vast majority of patients with myocardial

21   necrosis or acute ischemia whether they rea˜ly have

22   ischemia or myocardial necrosis at the time you have

1   to make the decision about which drugs you're going to

2   use.

3   And so I think when we do studies and say

4   we're going to separate acute MI from not acute MI as

5   an entry criterion, we're not studying the population

6   in the context in which the drug is going to be used,

7   and the results of therapy, I think, are almost

8   completely unknown by the practicing population.

9   It's even more compounded by the fact that

10   we don't know how to define acute MI anymore. Now

11   that we have markers of myocardial necrosis that are

12   much more sensitive, we're finding the majority of

13   people with acute necrosis do not have FT segment

14   elevation on the electrocardiogram. There is not

15   anywhere near complete overlap between CKMB and

16   treponeme measurements. The treponeme measurements

17   are prognostically much more valuable than the CKMB

18   measurements, and I think the sort of mythical

19   thinking that you can somehow know when you make the

20   decision which category the patient is in when we have

21   a national epidemic of an aging population many of

22   whom by their demographic characteristics are likely

1

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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CARDIOVASCULAR AND RENAL DRUGS

ADVISORY COMMITTEE

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86th MEETING

+ + +

Thursday, October 22, 1998

+ + +

The Advisory Committee met in the Masur
Auditorium, Building 10, National Institutes of
Health, Bethesda, Maryland, at 9:00 a.m., Milton
Packer, M.D., Chairperson, presiding.

PRESENT:

MILTON PACKER, M.D., Chairperson

ROBERT CALIFF, M.D.

JOHN DiMARCO, M.D.

MARVIN KONSTAM, M.D.

JOANN LINDENFELD, M.D.

1   to have coronary disease is -- just for radical

2   purposes I'd say it would be irresponsible in my

3   opinion to try to totally separate those two things.

4   Now, I agree that in retrospect trying to

5   look at who had positive enzymes and who didn't is

6   about the closest that you can come, but to do these

7   sort of puristic studies, put drugs on the market in

8   an increasingly confused clinical environment where

9   acute decisions need to be made with probably the

10   largest growing national epidemic, public health

11   problem, just doesn't seem to me to make a lot of

12   sense.

13   The second issue, which I think is what is

14   sort of related to that and what a lot of people have

15   brought up, is how in today's environment do we really

16   define safe and effective. Is safe and effective

17   defined as a theoretical concept of what possibly

18   could happen if doctors really always knew what they

19   were doing? In which case you could label a drug and

20   put it out there and people could use it as labeled

21   and it would be fine, or should there be some common

22   sense, not the extreme example that Jay brought up of,

1   you know, you've got a normal person and you have to

2   prove the drug doesn't do harm in them?

3   But, you know, everyone who develops a

4   drug spends countless hours of marketing people and

5   everyone else thinking about who really is going to

6   get treated. In my experience it's rarely exactly the

7   population that would have been labeled when the

8   calculations are made about the profitability and the

9   income stream generated from the high cost of R&D.

10   And so I think, you know, the

11   philosophical issue that's really being discussed here

12   is how do we really define safe and effective.

13   And the last sort of question is: what do

14   we really learn from mebefrodil? It was very safe and

15   effective in the population studied, in the studies

16   that were done.

17   Are there generalizable lessons from that

18   which should be thought about in relation to this

19   issue before us today?

20   CHAIRPERSON PACKER: Let me see if I --

21   this topic has the potential of being all consuming

22   and could take a whole day or many days, and let me

1   just say that I think that in defense of Jay, I think

2   the example that he put forward was intentionally

3   absurd because the idea is not to evaluate the

4   efficacy and safety of drugs in the patient population

5   diametrically opposite the one for an indication being

6   pursued.   It is to determine whether there is any

7   rationale to determining any experience in a patient

8   population who is extremely likely to get the drug if

9   it were to be approved.

10   And I think that everyone who has spoken

11   in the last hour on this issue has emphasized the

12   fact that this is a principle that needs to be paid

13   attention to, but given the incredible complexity of

14   the issue, it is very difficult to know how to craft

15   wording to provide specific guidance.

16   And I know that Bob has suggested that

17   future version of this document should attempt to do

18   so, and I guess since I'm likely to be involved in

19   those future versions, I'm a little bit nervous as to

20   what philosophical approach should be taken to define

21   an area which people intuitively feel should be

22   defined, but have trouble defining.

1   DR. TEMPLE: Well, I think you can do it,

2   and I think most of the comments that people have made

3   suggest how you might. For example, my response to

4   Rob's comment is that the committee might think that

5   any drug intended for the treatment of heart failure

6   ought to be studied at least to a degree in an acute

7   ischemic setting, as well as whatever other setting

8   they're looking at.

9   Okay. You're doing most of your trials in

10   people with chronic heart failure, but there ought to

11   be some attention to the acute situation.

12   I'm not endorsing or not endorsing it, but

13   I think that's the thrust of what he said.

14   Well, you could say that. I really don't

15   believe you'd do it in the same trial because I think

16   the endpoints would be different and the ability to

17   exercise would be different, but that's a nicety that

18   you could get to later.

19   But the general principle that people with

20   active ischemic heart disease who also have symptoms

21   of heart failure ought to be included in trials is one

22   that the committee could agree to.

Similarly, it could agree to the idea that any therapy ought to be thought of for its potential usefulness in people with and without abnormal ejection fraction. A conclusion might be that it's stupid to study it in one of those groups because the mechanism is inappropriate, but that's okay. It will have been thought of, and the labeling would point out that it doesn't make any sense to use it in those people or something like that.

I think you can tease these issues out, and it would be helpful if you did.

CHAIRPERSON PACKER: Okay. Nearly everyone wants to say something, and we clearly need to reach partial closure here.

Ray.

DR. LIPICKY: Well, just very short. I think the one extreme that was asked about was if you had a very restricted population that was studied, was that potentially approvable, and the answer was yes, with some caveats.

And I think on the other extreme, if there was only people who were said to have congestive heart

1   failure and they went the whole gamut and there was a

2   clear benefit, ignoring what it is that's being

3   measured, that is also potentially approvable.

4   These things we're talking about are

5   things that need to be thought about during the design

6   and conduct of the trial and are reasonable to analyze

7   and can generate hypotheses with respect to what other

8   things should be done, but I don't think any of them

9   are of the nature of if you do this it's okay and if

10   you don't do that it is not okay, because I can

11   conceive of circumstances where sort of anything would

12   be okay, but these, in fact, are the variables that

13   affect the decisions.

14   The thing that's missing from the section

15   is the statement like that. It isn't like what I'm

16   saying, but you know, there's no bottom line, and I

17   don't think there should be. I don't think it should

18   say if you don't study people with infarcts, don't

19   bother us, or if you don't study people with chronic

20   congestive heart failure for long periods, don't

21   ʰother us.

22   It   ought   to   say   these   are   the

1   considerations.

2   CHAIRPERSON PACKER: Okay.   I've been

3   ignoring a few people I just want to get. I actually

4   think we are reaching closure on this based on what

5   Ray just summarized.

6   Tom   and   Bert   and   we'll   take   a   few

7   additional comments, Lem, and see what we can do about

8   reaching closure. I had set aside about an hour for

9   this discussion, and we're getting there.

10   Tom.

11   DR. FLEMING: Just a general philosophical

12   approach.

13   I think in general we should be striving

14   toward   minimizing   the   differences   between   the

15   inclusiveness   of   our   eligibility   criteria,   our

16   labeling, and our actual use in clinical practice, and

17   it may well be that understanding of mechanisms can

18   give us some insights about settings in which we would

19   anticipate clinical efficacy or where we may be

20   concerned about safety, and that can well guide what

21   we would anticipate a labeling to be.

22   It's important then in the clinical trial

1 that we are inclusive, that we would then include with

2 the eligibility criteria those folks that we would

3 intend to be included in the labeling, and that's

4 where I think the statement in 116 and 117 is really

5 key.

6 It would trouble me, just to go on though,

7 if we anticipated clinical use to be much broader than

8 labeling. Certainly there could be some broader, but

9 if it were substantially broader and we were

10 restricting our labeling based on understanding of

11 mechanisms and concern about efficacy and safety

12 outside of that, it would trouble me if we had a

13 substantial experience.

14 So the principle as I would see it is we

15 should minimize the difference between the

16 inclusiveness of the eligibility, the labeling, and

17 the clinical use. They should be similar.

18 The second point --

19 CHAIRPERSON PACKER: Tom, let me just --

20 in order to accomplish that very honorable goal

21 req"ires two types of events or actually an agreement

22 amongst three parties. One is the sponsor; second is

1   the agency; third is the practicing physician.

2   We actually are not entirely capable of

3   influencing the third party. Maybe we should, but

4   we're not.

5   DR. FLEMING: Well, there are two major

6   steps here. One is how broad should the labeling be,

7   and I'm arguing it should be, in fact, as broad as

8   possible subject to our thought of where this agent

9   could be useful in clinical practice.

10   Now, if, however, we are broad in our

11 labeling, then our clinical trial should be done with

12 eligibility criteria that are inclusive, that are as

13 inclusive as we would anticipate our labeling

14 indication to be.

15   The second point that is somewhat

16 unrelated, but key, that's noted in Lines 122 to 124

17 here that I think is a point that I want to strongly

18 agree with here is that we need to evaluate the

19 intervention is a real world setting, and the manner

20 in which we expect it to be used in clinical practice,

21 and if there are concomitant meds. that are routinely

22 given and we anticipate our agent to be given in

1   addition to those concomitant meds., then the trial

2   should be designed so that the agent is evaluated in

3   the context of the use of those concomitant meds.

4   CHAIRPERSON PACKER: Okay. Bert, I think

5   you've had your hand up, and then we'll try to close

6   it.

7   DR. PITT: I think I agree with Ray's

8   formulation that there's not going to be an answer to

9   this, that it could be a narrow or broad approach

10   depending upon your view of the drug and the

11   mechanism.

12   I just have one nervousness that if we use

13   the wording as currently written here and just

14   sprinkle a few MIs in, then -- I think Lloyd touched

15   on this very nicely -- is we're not going to really be

16   able to say very much about it. It's going to give

17   you maybe a false assurance about the safety of this

18   drug.

19   So I think you have to be very, very

20   careful, and it will depend upon the mechanism,

21   depending upon the drug you're going to do, and we're

22   talking here in a vacuum really and in generalities

1   where really each case is going to be a very different

2   case depending upon what you're talking about.

3   The difficulty is to write a paragraph

4   that encompasses all of these things, and I think I

5   was very happy the way Ray formulated this in the end,

6   his last statements, because it is allowing us a very

7   broad approach.

8   CHAIRPERSON PACKER: Okay. Ileana and

9   then Lem.

10   DR. PINA: I want to turn it around a

11   little bit toward the sponsor to say that it would

12   perhaps be to the benefit of the sponsor if the drug

13   were going to be used in acute MI to study it in that

14   indication perhaps in a parallel trial as opposed to

15   all inclusive in one trial.

16   I'm also concerned that the sponsor could

17   be worried about safety in that population, and that

18   it may be reasonable to have a pilot study to test it

19   in that population, and then you can amplify your

20   entry criteria.

21   So that's just another way of looking at

22   the same issue.

1   CHAIRPERSON PACKER: Lem.

2   DR. MOYE: Ileana's recommendation for a

3   pilot study is a good one.

4   Something else that you might consider, if

5   you have two populations, one is a well targeted in

6   whom you believe the drug works, but is safe and

7   effective and is, in fact, the population for

8   indication and the population on which you size your

9   trial and do efficacy and so forth.

10   The second population is a population in

11   which you have no a priori of harm, but you need to

12   have some assurance that the drug is not going to be

13   harmful in a population in which the drug perhaps will

14   not be generally indicated, but would be used, you

15   might consider studying them in a controlled sense.

16   I mean, Lloyd suggested that, and very

17   helpfully said that, in fact, many of these patients

18   are considered in an uncontrolled or are included in

19   an uncontrolled fashion, and Marv pointed out the

20   difficulty with trying to interpret data from them.

21   Well, why not bring them in in a

22   controlled fashion, but differentiate the parameters

1   you use to judge safety? For example, in the trial in

2   which you're looking at the indicated population, of

3   course, the trial is sized for 15, 20, 25 percent

4   efficacy, but why not for this second population just

5   size it for a stronger signal?

6   You need far fewer patients in order to be

7   assured that you really don't have any real problem

8   with harm, and that could still be done in a

9   controlled setting. You could still draw reasonable

10   epidemiological conclusions from that.

11   CHAIRPERSON PACKER: Okay. We're going to

12   have a few closing comments. Udho, Rob.

13   DR. THADANI: I think in the days of

14   evidence based medicine, unless you open the inclusion

15   criteria broad, I think you should in the labeling say

16   which population was studied.

17   Drugs are not cheap. For example, take

18   ACE inhibitors or vasodilators. I know Bob is saying

19   probably safe in all patients. It may be safe, but it

20   may do nothing for the patient. If the EF is about 40

21   in patients with heart failure, I've not s en any data

22   in any trials to show that it improves survival,

1   reduces hospitalization in that group.

2   So are we going to tell all of the

3   patients who have EFs of 45, 50 that they should be

4   all on the drug? We may not be doing anything. I

5   think they're already on follow-up therapy.

6   So if those data are not available, I

7   think you should be in the label these patients, and

8   the reason drug studies are designed to include very

9   low EFs or below 40, because then your sample size

10   goes smaller and you can show efficacy, and if you're

11   not going to show any benefit, why give the drug?

12   So I think my feeling would be in the days

13   of evidence based medicine, it should clearly

14   specified.

15   At the moment hospital charts are being

16   audited, and if somebody's EF is 30, why did not you

17   use Drug A or B because that's not a good practice of

18   medicine? But physicians will do what they will, and

19   I think if there is no data, then there should be

20   controlled trials in that population.

21   I give you an example of the NIH study

22   going at the moment to see patients on ACE inhibitors

above EF of 40 percent in eight, 9,000 patients to see if it does any good or bad. So I think we should do that.

If you're going to allow just routine use, extension of the trial to everybody, I think it might be not doing service to the public.

CHAIRPERSON PACKER: Rob.

DR. CALIFF: Go ahead.

CHAIRPERSON PACKER: Okay. Let me --

DR. COHN: Can I just make one comment?

CHAIRPERSON PACKER: Okay.

DR. COHN: Just to bring closure to this, you know, the fact that inclusiveness of patients in a trial does not necessarily mean that labeling should be inclusive. I think that's actually a terrible misperception because, I mean, just think about an old example.

If you put in thousands of people with fever and give them penicillin and demonstrate that there's a reduction of fever, it really shouldn't lead to labeling that fever should be treated with penicillin. We're a little more sophisticated.

1   And I just don't think that -- I just

2   think we have to become much more specific in our

3   labeling. Otherwise we're going to just perpetuate

4   this idea that everybody responds the same to a drug.

5   CHAIRPERSON PACKER: That needs to be done

6   in a well thought out fashion as part of the original

7   developmental plan as opposed to in a subgroup

8   analytical approach after the trial has been

9   completed.

10   DR. COHN: Yeah, and that gets back to

11 doing a targeted population.

12   CHAIRPERSON PACKER: No, that's fine. I

13 just want to make sure that the misconception was not

14 conveyed that one could go back, try to find some

15 population that seemed to respond to it and pursue a

16 labeling for it.

17   DR. COHN: No, it's hypothesis generating.

18   CHAIRPERSON PACKER: That would be

19 hypothesis --

20   DR. COHN: -- when you put a large

21 pop·lation in.

22   CHAIRPERSON PACKER: Bob.

1   DR. TEMPLE: I mean, people presumably go

2   about this in an orderly way. You don't do your

3   10,000 patient mortality trial right off the bat.

4   First you look to see in various subpopulations

5   whether you're getting the kinds of pharmacologic

6   effects that make you optimistic.

7   So you do all of that kind of stuff. You

8   perfectly well can look at subgroups, even unplanned

9   ones, in early studies, and then you go about it.

10   I mean there's a dichotomy being drawn

11   that seems to me somewhat wrong. Of course you don't

12   assume that any mechanism works in any population, and

13   to some extent what I hear most people saying is you

14   should examine whether the -- you should consider the

15   intelligent distinctions between patient populations

16   and either not study some of them because it doesn't

17   make sense or explore whether the drug works as you

18   think in important distinctions.

19   Getting wrapped up in whether a drug could

20   be approved for a narrow population or a broad

21   population isn't really the main issue because, as Ray

22   said, either is possible, but what I think you want in

1   the guidance is intelligent ways to think about these

2   problems.

3   And Jay has certainly put his finger on

4   it. You want to use distinctions that, as best you

5   understand things, make sense now with the full

6   knowledge that what you understand will change over

7   time, but you do the best you can, and you make the

8   distinctions that are now known to be sensible like

9   between people who are in the middle of an ischemic

10 event and people who are not.

11   We all seem to think that's a sensible

12 distinction, and another sensible distinction at least

13 for many drugs is whether a person has a normal

14 ejection fraction or not, and there may be others that

15 could be defined over time.

16   Where there are sensible distinctions, it

17 may be necessary to study them separately, and a wide

18 variety of other etiologic and concomitant therapy

19 characteristics can be looked at as subsets because

20 you really can't do much better. You can't study

21 every group.

22   DR. FLEMING: But your trial, Bob,

shouldn't be studying a more narrow group than you're

labeling, than you intend with your labeling.

DR. TEMPLE: No, I agree with that. On

the other hand, you know, I think just to follow up

Jay's example, if you include a wide variety of people

and a third of them are people who really wouldn't be

expected to respond, but you've included them, you may

get an overall favorable result, but it really may not

apply to one subset that you've included.

You can make a study strong enough to

overcome the fact that you've included some people

you've just carried along. You don't get away with

this just by failing to have the inclusion of

inappropriate people to defeat the study. You still

do need to look at intelligent subsets of the

population, and you should plan to do that.

CHAIRPERSON PACKER: Let me --

DR. TEMPLE: The trouble is our view of

what's intelligent changes as we learn more, but

that's okay.

CHAIRPERSON PACKER: Let me put a bookmark

here, and at least get a committee consensus on one

1   specific issue to Ray and then have Ray respond, and

2   that is --

3   (Laughter.)

4   CHAIRPERSON PACKER: Whatever.

5   I think that almost everyone who has

6   commented on this important topic has suggested that

7   a part of the problem that exists right now could be

8   addressed by Tom Fleming's suggestion to minimize the

9   differences between the patient population studied and

10   the indication being sought, which relates to the

11   question we had to Ray earlier, because right now

12   frequently sponsors get a much broader indication than

13   the patient population being sought, i.e., ejection

14   fraction is not even mentioned in the labeling even

15   though only patients with a low ejection fraction are

16   measured or patients with a low ejection fraction are

17   evaluated.

18   Would it be a sense of the committee --

19   and I do not want discussion on this -- that the

20   indication section of labeling be more highly

21   reflective of the patient population being evaluated?

22   Does anyone disagree with that?

1   And, Ray, that would at least give you our

2   sense that we would like to see the indication

3   sections be more specific, particularly as it relates

4   to major categories of disease.

5   DR. LIPICKY: It will come up again when

6   you get farther into the guideline, and I think I

7   would like to comment on that at that time.

8   CHAIRPERSON PACKER: No problem.

9   DR. LIPICKY: But you can bring this to

10   closure.

11   CHAIRPERSON PACKER: Terrific.

12   The next section, which is Section 3 on

13   clinical pharmacology, we had planned on having Dan

14   Roden discuss it. Dan is delayed this morning, and we

15   will try to get his comments later on.

16   Let me just, if I could, in literally a

17   minute summarize the fact that what this section does

18   is it describes a number of processes that a sponsor

19   might follow in order to characterize a drug in terms

20   of its pharmacological actions.

21   And the division would like to emphasize

22   that characterization of a drug is highly desirable,

1   but that the surrogates that are normally used to

2   characterize a drug are not necessarily the primary

3   endpoints for clinical trials and, therefore, are not

4   necessarily the basis for approval, but are the basis

5   for adequate characterization.

6   Therefore, the characterization of a drug

7   is a necessary, but not sufficient, component of drug

8   development, and the degree of characterization should

9   be appropriate to the agent being evaluated and is a

10   worthwhile point of discussion with the division.

11   And that is the overall summary of that

12   section.   One point which I want Barry Massie to

13   comment on is there has always been a lot of

14   discussion   in   the   characterization   of   the

15   pharmacological effect about dose response. There's

16   been   a   lot   of   discussion   about   dose   response

17   relationships   in   clinical   pharmacology   studies   in

18   distinction to dose response relationships to major

19   trials with clinical endpoints, with clinical measures

20   as their endpoint.

21   And the difficulty that exists is that the

22   surrogates   which   are   used   in   clinical   pharmacology

1   studies that might be used to define dose response may

2   or may not relate to the clinical endpoints that are

3   used, and that specific issue is addressed in Section

4   3.2, and therefore, the guideline now states that it

5   is important to evaluate more than one dose whenever

6   appropriate in major trials simply because the

7   evaluation of more than one dose in clinical

8   pharmacology studies may or may not be adequate.

9   Barry has previously, which is why I want

10 him to comment, has discussed the concept of a pyramid

11 where a large number of doses might be evaluated in

12 clinical pharmacology studies with fewer and fewer

13 doses as the endpoints in the clinical trials become

14 more clinically relevant.

15   Barry.

16   DR. MASSIE: Yeah, and pyramid sounds

17 awfully big, but I think the concept is certainly an

18 important one and one that Ray has, of course, pushed

19 over the years quite strongly, which is that generally

20 we have no idea what the right dose is of a drug. The

21 clinical pharmacology evaluations can put u⁻ in the

22 ball park, but probably not narrow it down, and I can

1   think of very few development programs where at one

2   point or another people haven't looked back and said,

3   "I wish I had known about the safety or the efficacy

4   of a dose I didn't study." Some have collapsed as a

5   result of not looking at that type of data when they

6   may be very good drugs. In fact, some have been

7   resurrected only because they looked at more than one

8   dose.

9   What we have here is, of course, the

10 conflict between what's desirable and what's

11 practical, but I think in general, I think I agree

12 with some paraphrasing of some statements I made

13 earlier, which is, yes, if we have a clinical

14 pharmacology marker that makes sense, and we're now

15 facing an era of drug development where we may not

16 have any clinical pharmacology markers that are going

17 to help us out, but when we do, we should study

18 several doses, and I think we should carry at least

19 two doses into our major clinical trials.

20   And my offer, which I'm not sure that Ray

21 would pick up on, would be that we somehow or another

22 loosen the statistical penalties of dropping groups,

1   but starting with several; that we allow interim

2   analyses to determine the most effective dose along

3   the way in order to somehow or another reduce the cost

4   of getting this very important information.

5   CHAIRPERSON PACKER: We will deal with

6   this in a very specific part of today's discussion,

7   and there are many who have spoken to this issue, and

8   we will speak to this issue more specifically.

9   DR. MASSIE: So that's the way I would get

10   to my pyramid. Look at several doses, figure out your

11   best clinical pharmacology marker, look at something

12   on the high end, the middle end, and maybe the low

13   end. Bring those into clinical trials, and somehow or

14   other hopefully one can then narrow things down or at

15   least get the right answer at the end.

16   CHAIRPERSON   PACKER: This   is   a

17   sufficiently   important   issue,   and   it   is   likely

18   actually to get submerged later on. Let's take, if we

19   could, just a few minutes to talk about one of the

20   imposing things that sponsors frequently encounter is

21   that if they do multiple doses, there's a

22   multiplicative effect on sample size not only because

1   of the fact that you're studying more than one dose,

2   but because there may or may not be a statistical

3   penalty for multiple comparisons within a trial.

4   And we need to at least discuss this point

5   very briefly because it's pivotal to the feasibility

6   of dose response studies, and, Rob, why don't you

7   start off? And, Tom, I'll ask you to speak to this as

8   well.

9   DR. CALIFF: Yeah, this issue is mixed up

10   with several key factors from my perspective. Again,

11   I'm going to be a little outrageous here, hopefully to

12   stimulate discussion, but the key factors to me are

13   the increasing cost of developing clinical

14   therapeutics, encouraging people to do the right

15   thing, and matching the dose and use of a drug to

16   where it's really going to be used in practice.

17   So I guess the outrageous statement would

18   be that the way things have gone, I think sponsors

19   have increasingly been encouraged to be more and more

20   certain about more and more irrelevant characteristics

21   of drugs because of the huge cost of really finding

22   out the answers that will improve the outcomes of

1   patients.

2   And I think what we need to do is to try

3   and figure out how we can encourage people to do the

4   right thing.   I would rather be a little more

5   uncertain about a clinical outcome study in a relevant

6   population than to be absolutely certain, again, as

7   with mebefrodil, in a population which is not terribly

8   relevant to the broad group of people who would

9   actually be treated in practice.

10   So I agree completely with what Barry

11   said.   We really don't have surrogates in heart

12   failure that are known to be predictive of what the

13   ultimate impact of a drug will be on a patient's

14   longevity or quality of life, but surrogates are

15   absolutely essential in the early developmental phase

16   to narrow down to several doses.

17   If we retain the strict criteria we

18   currently have statistically and you have more than

19   one dose in a large clinical trial, the costs become

20   so high. We're seeing good therapies now being put on

21   the shelf by companies because relative to development

22   -- my favorite one right now is cosmetic drugs where

1   you make a huge profit with small studies. It's just

2   not worth it to spend the money.

3   And yet here we have the most important

4   public health epidemic, and we're out pricing. So I

5   would encourage our statistical colleagues to help us

6   think through how we can put in rules that will make

7   it easier for companies to do the right thing.

8   Maybe it does require not sticking to a

9   less than one in 10,000 chance that you could be wrong

10   when it's real clinical outcomes that are being

11   studied.

12   CHAIRPERSON PACKER: Tom.

13   DR. FLEMING: Rob, just a couple of key

14   points. Just very quickly on the first relative to

15   the surrogates, I would concur with very much of what

16   Rob said throughout that the understanding of

17   mechanisms of action can be extremely helpful and

18   often most directly identifies what biological

19   mechanisms or biological measures are likely to be

20   impacted, and these are our surrogates.

21   And use of those surrogates can be

22   extremely helpful in early development studies and

1   helping to guide dose selection, et cetera.

2   Yet because there are a multiplicity of

3   different causal mechanisms of the disease process, as

4   well as of the intervention intended and unintended,

5   the ultimate clinical trial needs to focus on effects

6   on clinical endpoints.

7   Relative to this issue of multiple doses,

8   we could have a long discussion. In the interest of

9   trying to keep it short, I believe that adjustment is

10   necessary, but I would argue for adjustment that makes

11   sense.

12   For example, if you had two doses against

13   a control in a single study, and what we're typically

14   trying to preserve whether it's a one-sided .025 or a

15   two-sided .05, both of those share the property that

16   it's a .025 false positive error that we're trying to

17   preserve. So let me state in terms of that one-sided

18   .025 standard.

19   If you had a single dose against a control

20   and you got .02, you would hit that magical boundary

21   for a standard for strength of evidence. If you had

22   two doses against a control each of which were, quote,

1   unquote, significant at the .02 level, if you did a

2   correction for having done two requiring half of .025

3   or .0125, neither of those would be formally

4   statistically significant, but that's a bit illogical

5   because there's stronger evidence with two doses, both

6   significant at .02, than just one dose significant a

7   .02.

8   And my argument is we are not really

9   applying the statistical guidelines in a way that make

10   practical sense. I believe you do have to adjust for

11   the existence of the second dose. To my way of

12   thinking, the analysis ought to be a comparison of

13   each dose against control and whether or not that is

14   viewed to be individually statistically significant as

15   based on our standard strength of evidence, which is

16   .025.

17   But then at the time that we look at all

18   of the data, which is typically right here at an

19   Advisory Committee level, then all of the information

20   needs to be taken into account, and the existence of

21   these other doses do come into play.

22   So that, for example, if I have a low dose

1   that's significant at the .02 and there exists a high

2   dose that's also significant at the .02, recognizing,

3   of course, the correlation because of the common

4   control, my formal or informal meta analysis should be

5   done and should recognize that the existence of the

6   high dose data doesn't weaken the low dose data. It

7   strengthens it.

8   And statistical analyses through formal or

9   informal meta analyses do allow us then to take into

10   account all of the multiplicity of testing, so to

11   speak, or the multiplicity of experience that we have

12   with multiple doses.

13   So I guess bottom line is -- and I think

14   it gets at what Barry's advocating -- if you do a

15   study with two doses, I look at each of the

16   individuals against a control individually to see

17   whether or not that is evidence of that particular

18   comparison being significant.

19   I don't try to control the experiment wide

20   error rate, but I do adjust for this multiplicity of

21   experiences, but do so at an Advisory Committee point

22   when you're looking at the totality of information.

1   Does the totality of information provide convincing

2   evidence of efficacy?

3   CHAIRPERSON PACKER: Lem.

4   DR. MOYE: I feel compelled to respond.

5   Is alpha conservatism necessary all of the time?

6   Certainly not. There are circumstances where you do

7   pilot studies, where you do hypothesis generating

8   work. I cannot resist doing hypothesis generating

9   work, as I'm sure many of my colleagues here cannot.

10   And so in some circumstances you call it

11   hypothesis generating, and you carry out your

12   analyses.

13   However, in circumstances where you are

14   identifying a new intervention for a large patient

15   population, you have to provide adequate protection

16   for the release of a placebo poison, and by placebo

17   poison, I mean a medication that is presumed to be

18   effective, but in fact is not, but the medications do

19   have side effects.

20   And so by making the Type 1 error, you are

21   essentially releasing a placebo poison. There has got

22   to be adequate community protection for that, and the

1   best protection, a protection that we are unhappy with

2   and I myself sometimes, is Type 1 error rates.

3   Having said that, I think I can say that

4   there are some alternative procedures that are now

5   becoming available and seeing increased use that may

6   ride to the rescue.

7   One of them is the notion of dependency in

8   your measures of events, and we've seen some examples.

9   One was in teguelin, I think, where they actually did

10   some computations providing a very defensible

11   correlation between events occurring at one

12   intervention or another intervention, and were,

13   therefore, able to conserve Type 1 errors so that they

14   had an adequate error rate leading to fairly lower

15   sample size and, therefore, an executable study.

16   And also some work that hopefully will be

17   out in the literature which suggests that, in fact,

18   you can, by looking at the total experimental alpha

19   level and setting that at a somewhat higher rate than

20   .05, but specifying some bounds on the alpha that you

21   would sent for the primary endpoint, that there is the

22   -- one can make a very statistical alpha conservative,

1   defensible argument for positive studies not only

2   where one dose is positive but another does is

3   negative, but where the primary endpoint finding may

4   be nonsignificant, but the study could be considered

5   positive because of a positive finding for a secondary

6   endpoint.

7   I mean, if that analysis holds up and is

8   just coming into the literature now, if the analysis

9   holds up and many of my mathematical and stat.

10   colleagues agree with that, then there is ample

11   opportunity here to, number one, continue to hold as

12   paramount the notion of being conservative about Type

13   1 error, but having new ways to use it so that you

14   have adequate alpha to expand on in these complicated

15   experimental environments where you have multiple

16   interventions and multiple endpoints.

17   CHAIRPERSON PACKER: Okay. The goal here

18   is not to get into a detailed discussion of this.

19   It's more to let people simply clarify their overall

20   concepts about this.

21   Ray?

22   DR. LIPICKY: Well, very quickly, I guess,

1   I'm not quantitatively very competent, but the

2   discussions in this area generally focus upon making

3   two points comparisons and talk about spending alpha

4   and so on and so forth, and I think that framework of

5   reference is totally wrong.

6   When you have more than one dose of a

7   drug, the question, I think, should not be is this

8   data point different from the other data point and how

9   do I have to pay a statistical penalty. The question

10   should be devoted to: is this dose related?

11   And I think that most of the things that

12   deal with trying to distinguish one number from

13   another number are far less powerful in terms of what

14   they require than when you take all of the data

15   together, and I'd be willing to impose model dependent

16   analyses on that information.

17   And it's not very well dealt with, and

18   just as an example, in the hypertension arena, I know

19   James Hung has a paper published on doing an analysis

20   where you can conclude that the trial found a

21   combination product where, in fact, both ingredients

22   contribute to the effect. This was published a number

1   of years ago, very powerful.

2   Even though every cell doesn't distinguish

3   itself from another, I have never seen anyone analyze

4   a factorial trial that way. They always send them in

5   comparing one cell to the other and talk about the

6   stuff, even though we said this is how you should do

7   it and we'll accept it.

8   So there is a lot of miscommunication in

9   this area, and it is not well handled, and it is not

10   internalized anywhere along the line, and I would like

11   to see a lot more discussion about that, but it's very

12   technical and very difficult.

13   CHAIRPERSON PACKER: All right. We're

14   going to get Lloyd and then Bob, and then we will

15   close this topic.

16   Actually I want to have Dave DeMets talk

17   about surrogates as a closing statement, just to

18   summarize your views on that.

19   DR. FISHER: Yeah, we have very competing

20   things here. Later today we'll probably hear that if

21   you have a serious irreversible endpoint -- in fact,

22   it's in the draft guidelines -- we'll have to go to

1   the level of two trials, the .0025, and here we're

2   talking about weakening our level of proof.

3   I've come to the following conclusions.

4   I'll give Bob Temple a little clue about some things

5   I'm going to say at a Pharma meeting so that he can

6   start thinking about it.

7   Number one, our statistical models, as

8   nice as they are, don't really adequately mirror the

9   level of evidence in its entirety, and I doubt that

10 they will within my lifetime.

11   But having said that, I think there's a

12 number of ways we can begin to address things. For

13 example, sponsors can design parallel group trials,

14 but actually go with just one of the doses after

15 relatively little evidence, say, if you've just ruled

16 out big differences in certain ways. In other words,

17 you don't have to go to where you show each dose is

18 definitive.

19   It might be a quarter or a third of the

20 way through, and if you don't see huge differences,

21 you may want to pick the high dose, say, the usual

22 philosophy, to be sure we get our effect, and then

1   come back in Phase 4 and have a non-placebo controlled

2   and get more information.

3   In other words, the learning does not have

4   to stop at the time of approval.

5   Secondly, by our usual paradigm, let's say

6   we have an endpoint where we can ethically do two

7   trials. We have one positive trial and one that is

8   not quite positive, and we look at it, and we say, you

9   know, "Sorry, but this just misses." The more that I

10   think about it, it doesn't make sense to me to require

11   someone to go out and do an entire new trial at the

12   .05 level, which is typically the way things are done

13   now.

14   Why can't we say if we get a certain

15   amount of additional information, that standing alone

16   would have relatively little statistical power, say,

17   a P of .2 or something, but in conjunction with

18   everything else would push us over the edge?

19   And I think we really need to start

20   thinking about this very seriously because I think it

21   can save tremendous resources, and that's what we'll

22   be talking about in a few weeks.

1   CHAIRPERSON PACKER: Just let me ask Lloyd

2 a question because part of what I want to talk about

3 is not just lessening the penalties for the end of the

4 trial having multiple groups, but ending the penalties

5 for stopping a group early, like what you just brought

6 up.

7   Because I think it has been interpreted

8 that there is a statistical penalty in general to

9 start with three groups and drop one because it

10 doesn't look as good as the other one or it looks the

11 same later, but I think that is the most cost

12 effective strategy.

13   If you're going to go with three groups to

14 the end, it's still going to cost a lot of money even

15 if you lower the threshold a little bit.

16   DR. FISHER: I don't want to get too

17 technical because Milt doesn't want that here and this

18 isn't the right audience, but you know, statisticians,

19 of course, are not magicians. I mean, we operate

20 within the constraints of mathematics, as Dr. Moye

21 eloquently reminded us a number of times.

22   But having said that, there are ways you

1 can actually pay appropriate penalties for this, and

2 there's a number of tests. It always amazes me that

3 with two arms, for example, people often don't do

4 tests where you assume at least a monotone response of

5 some sort for your efficacy. They often do the

6 equivalent of one-way analysis of variance, but there

7 are more efficient things that can often be done, and

8 my suspicion is, although I haven't done the

9 computations because I haven't had a real trial to

10 work on; my suspicion is that if you do this under

11 most scenarios, the penalty will be relatively small.

12 It certainly will not be anywhere near equivalent to

13 keeping all of the arms.

14   CHAIRPERSON PACKER: Bob.

15   DR. TEMPLE: Studying multiple doses in

16 short term, symptomatic studies is not a big

17 development problem, and it can be done. It's done in

18 hypertension all the time, and I don't think that's

19 the problem.

20   The problem is with large trials where you

21 are talking about thousands of patients, and I think

22 we ought to take a better look at how much we really

1   need multiple doses.

2   Ray will roll over about this, but it's

3   worth reminding everybody. I was making a small list

4   that for beta blockers, lipid lowering drugs, ACE

5   inhibitors in heart failure, essentially hypertension

6   trials, we have not studied single doses. Sometimes

7   we've titrated to an endpoint. Sometimes you've just

8   given a big slug. I mean the timolol post infarction

9   trial probably is the dose five times what you need to

10   get adequate beta blockade, and that's not a big

11   problem because there's not a lost of dose related

12   toxicity or, put another way, the results were so good

13   we don't care that much if the results would have been

14   a little better if we had a bigger dose or a smaller

15   dose, and it was practically very difficult to study

16   multiple doses.

17   There are some drugs with minimum dose

18   related toxicity where it makes the most sense to

19   study a high dose. There are other drugs where

20   there's a bleeding risk or something if you put the

21   dose where you might want to be much more cautious.

22   But how you be cautious might be a

1   different way. For example, you might start a high

2   dose group of some kind of anti-platelet drug and a

3   low dose group just to see if there was excess

4   bleeding in the first 1,000 patients, and if there

5   wasn't, you might drop the low dose group and go with

6   the high dose group.

7   I'm not sure what the penalty should be

8   there, but it can't be very large. You've only

9   exposed a small fraction of your population, and if

10   you wanted to, you could even not do any interim

11   efficacy look at all. You could just look at

12   bleeding.

13   So there probably are a lot of ways to

14   design trials to answer certain intermediate questions

15   that don't have big penalties, but I think we need to

16   think about why we always want two doses. There are

17   some drugs that aren't very dose related toxic, and

18   maybe those are cases where we should just eat the

19   uncertainty and go with a good, big dose, as we always

20   have in the past, by the way.

21   CHAIRPERSON PACKER: Bob, and again, the

22   goal here is not to have this go into a long

1   discussion about the desirability or nondesirability

2   of more than one dose.

3   I just want one -- it may be appropriate

4   to simply emphasize what Barry said earlier, and that

5   is that it's not so much that one requires multiple

6   doses in all cases, and it isn't so much what the

7   agency would or would not do if one didn't have

8   multiple doses.

9   I think Barry's point is that the

10   examples, particularly in the area of heart failure,

11   where it's been in the sponsor's interest to do

12   multiple doses in a clinical evaluation trial --

13   DR. TEMPLE: Only in the short term

14   studies.   The large studies almost never have more

15   than one dose. The large outcome studies have usually

16   been one dose.

17   CHAIRPERSON PACKER: Well, that may be

18   part of the problem. The risk to benefit relationship

19   in heart failure may not necessarily parallel the risk

20   to benefit relationship in other therapeutic areas,

21   and the number of times when a sponsor has regretted

22   not evaluating another dose in their clinical efficacy

1   trials is so numerous as to be unbelieved.

2   DR. TEMPLE: But the point is, Milton, we

3   have enough experience now to know that for ACE

4   inhibitors it may not matter much, and for ionotropes

5   it may matter a lot.

6   I mean sometimes you can use that kind of

7   information to design either a multi-dose trial or a

8   non-multi-dose trial. It may vary from one situation

9   to another.

10   I don't think we should reflexly say,

11   "Well, I know you're planning a 20,000 patient study,

12   but really you've got to make it 30." That just may

13   defeat the ability to do any study at all.

14   CHAIRPERSON PACKER: Ray?

15   DR. LIPICKY: Well, only to respond to

16   what's been said. It could be that the beta blocker

17   positive effect would be three times the effect that

18   you see. You just don't know that. So all you know

19   is it works.

20   DR. TEMPLE: True.

21   DR. LIPICKY: Okay, and you don't know if

22   you couldn't get a better effect. That's one.

1   DR. TEMPLE: Right.

2   DR. LIPICKY: Two --

3   DR. TEMPLE: But, Ray, at least you know

4   that because somebody bothered to do the study.

5   DR. LIPICKY: Well, no, no, no. That's

6   fine, but the question is not what can you get away

7   with.   The question, just like with respect to

8   etiology of heart failure, is what are the decision

9   making factors that you ought to think about. That's

10   what's in the guidelines.

11   You can always get away with much less

12   than what is intelligent and rational, right? ACE

13   inhibitors you know now are probably not -- the

14   highest tolerated dose is probably okay, but you know

15   that on the basis of a single study, and that is

16   something like the 12th or 13th study that studied

17   irreversible harm in patients with heart failure.

18   So it took that long to find that

19   information out. It would have been nice to know that

20   up front.   That would have been a public health

21   benefit.

22   So all of those things are true, but

1   that's not what we're talking about, I don't think,

2   for the guideline purposes what you can get away with.

3   We're talking about what things you ought to think

4   about.

5   DR. TEMPLE: It's bi-directional, Ray,

6   though. The bias shouldn't always be you should study

7   as many doses as possible. You ought to be thinking

8   of whether this is a case where you should make the

9   study larger and only study a single does because may

10   have a benefit, too. You've got to think both ways.

11   CHAIRPERSON PACKER: Dave, do you want to

12   have any concluding comments on surrogates?

13   DR. DeMETS: Well, I think that what I

14   would say is similar to what Tom says since we

15   published a paper a couple of years ago on this. I

16   think in heart failure we have clearly demonstrated in

17   any disease area I know that there's no reliable

18   surrogate outcome measure to predict clinical effect

19   on clinically relevant outcome.

20   And so if that's true, then you have a

21   problem in designing or picking the right dose because

22   you can get in the ball park maybe based on toxicity,

1   clinical outcome.

2   DR. THADANI: When you drop the dose, it

3   runs the danger that it might be the effective dose.

4   I mean you're presuming the high dose is safe, and

5   you're dropping the low dose.

6   DR. DeMETS: I'm not presuming anything.

7   I want to start out with two, three doses. I'm

8   suggesting, and look to see what's happening.

9   DR. THADANI: Why drop them? Carry on

10   with -- if safety is not the issue, just carry on with

11   all of them.

12   DR. DeMETS: If you can afford four N, do

13   it.

14   CHAIRPERSON PACKER: Why don't we move

15   forward? The next section we'll be talking about is

16   the Section 4, which is the design of major studies

17   Who wants to take a break? Anyone?

18   PARTICIPANT: No.

19   CHAIRPERSON PACKER: I guess not.

20   PARTICIPANT: I just did.

21   (Laughter.)

22   CHAIRPERSON PACKER: We're going to move

1   on to Section 4. I want to emphasize, again, the goal

2   in reviewing this document is not to review every

3   paragraph or every sentence. This discussion has been

4   organized in order to proactively identify areas of

5   controversy.

6   So there are many parts of this document

7   which are really not very controversial and,

8   therefore, we are just not discussing today.

9   So we've highlighted already in Sections

10   1, 2, and 3 the areas of controversy, and these are

11   the areas which are likely to be modified in

12   subsequent versions of this document.

13   In terms of Section 4, design of major

14   studies, we've asked Lloyd Fisher to review and

15   summarize the major issues here.

16   Lloyd.

17   DR. FISHER: Okay. Well, I was asked, and

18   I'm prepared to talk about -- I guess I can talk about

19   the whole thing. I'll look at my notes, but I was

20   told to go up to about Section 4.4.

21   The reason I mention that, was somebody

22   else assigned the rest of Section 4?

1   CHAIRPERSON PACKER: No. You've got all

2   of four, but, you know, it's okay.

3   DR. FISHER: The baseline evaluation, the

4   population we've talked about quite a bit. In the

5   introduction paragraph I note the range of the useful

6   doses is supposed to be defined. We just discussed

7   that. I won't go into that again.

8   In the baseline evaluation period, I

9   wanted to bring up the issue. It says here the idea

10   is to minimize noise imposed, and this, of course,

11   developed more classically when most of the efficacy

12   was exercise testing, and we wanted stability in

13   exercise testing and relatively stable heart failure.

14   I might point out that when we go for

15   mortality or mortality plus serious morbidity, the

16   issue is much more complex, and since there will

17   inevitably be deaths and a fairly long run-in period,

18   and this comes up again later in the document under

19   analysis, it's difficult to know how to evaluate those

20   data.

21   Certainly one looks at it to see that the

22   mortality rate is consistent with the rest of the

1   study once you randomize. Otherwise you run the risk

2   of having a very high risk set taken out early, but

3   probably in general it's not a good idea if it's a

4   mortality and/or serious morbidity study actually to

5   have a long baseline evaluation period because we

6   don't have any comparisons for those endpoints, those

7   deaths.

8   And so Dr. Temple's enrichment design is

9   very nice in a variety of settings, but it's probably

10   not too desirable here.

11   I won't say anything about placebo

12   controls and blinding or the need for randomization.

13   I think we've all been schooled in this long enough

14   that we realize that it's very desirable unless

15   there's some particular reason it can't be done.

16   There's a section on the use of background

17   therapy. In general, I think most of the trials,

18   unless the drug is intended as a replacement for some

19   of the standard background therapies -- will have

20   standard background therapy because the investigators

21   will feel that it's unethical not to avoid it.

22   So perhaps this is not as debatable as it

1   might be. There is the statement, "Generally the use

2   of background medications should be of little

3   consequence if the trial is appropriately designed."

4   I don't know how you can necessarily conclude that.

5   Often the background therapy actually is whatever the

6   patient can take in terms of digitalis, diuretics, ACE

7   inhibitors, possibly beta blockers now.

8   And since the background therapy is not

9   randomized, it could have a large effect, and we

10   wouldn't know it at the end of the trial unless we

11   have an observed treatment interaction.

12   There's a discussion of the use of

13   positive controls which are very difficult, to say the

14   least. In that paragraph it might be added that

15   occasionally you can get some idea of how the

16   historical control did against placebo and then try to

17   integrate that knowledge into your evaluation.

18   Granted it's historical, but at least you've taken

19   into account the variability in the placebo controlled

20   trials or controlled trials of your active control in

21   the current trial, and the committee saw this when

22   lapidogril was discussed.

1   Crossover designs, as stated, are very

2   difficult in general and problematic, but I think in

3   heart failure it's much worse than in general because

4   the substrate changes so often, and it's really a

5   horrible idea.

6   Dr. Temple isn't in favor of it in

7   mortality trials. There does tend to be a certain

8   carryover effect.

9   (Laughter.)

10   DR. FISHER: Open label run-in periods I

11   just discussed, and that takes us up to five.

12   CHAIRPERSON PACKER: Lloyd, before opening

13   this up for discussion, let me just make sure that I

14   have identified correctly the areas of the document

15   that you think require some either modification or

16   clarification. Can you just summarize that again?

17   DR. FISHER: Well, the either open label

18   run-in or baseline evaluation period, I think, can be

19   more problematic here in part for the reason crossover

20   trials run into problems. You have this change in

21   substrates. So even if you only include pe ple stable

22   for a certain length of time, that doesn't remotely

1   imply that they'll continue to be stable for a very

2   long time period.

3   And I haven't actually looked at the

4   natural history to see if the exacerbations looked as

5   if, say, they followed the time to some exacerbation

6   was exponential. If it is, that implies what's called

7   a memoryless property.

8   But in point of fact no matter how long

9   they're stable, you don't really get any relevant

10   information about what's going to happen later, and

11   certainly when you have the open label run-in, if your

12   baseline evaluation includes time on the drug, then

13   you run into all kinds of problems for the analysis if

14   you have enough individuals and enough exposure that

15   you get many deaths at all.

16   CHAIRPERSON PACKER: I think what this

17   paragraph should say is that the concept of a baseline

18   evaluation period and its length really needs to be

19   individualized according to the kind of drug being

20   developed, and also to the primary endpoints being

21   evaluated.

22   As you said, in the past when, for

1   example, exercise was a primary endpoint, that

2   baseline evaluation period was very important.

3   DR. FISHER: And it also depends, of

4   course, on the severity of the heart failure or the

5   patient characteristics. You know, if it were a Class

6   1 or something, then you're not going to get that many

7   certainly not fatal events, and it might be more

8   reasonable.

9   But as you get up into the twos and

10 threes, then the issue can be quite substantial.

11   Hear Bob Temple on this.

12   CHAIRPERSON PACKER: Yeah, Bob.

13   DR. TEMPLE: We've seen some baseline run-

14 ins where the reason was to see if patients could

15 tolerate the drug. Your alternative, of course, is to

16 just randomize everybody and drop them, but then

17 you're dropping large numbers of patients.

18   The CAS study actually, the CAS studies,

19 I mean, provided one way of solving that problem. I

20 don't know if everybody remembers this, but in the CAS

21 studies, you had to have a 70 reduction in 'PBs in

22 order to be randomized.

1   Well, the first studies took patients

2   fairly recently after an MI and made sure that they

3   had these responses, and there were a lot of deaths in

4   that group, but of course, nobody could know what to

5   make of that because there was no comparator group.

6   CAS II said we're worried about this.

7   Maybe the drug is killing people off during the

8   initial peak treatment. So they did a randomized run-

9   in. In other words, they got a mortality result, and

10   I don't know if people remember this, but the

11   ethmozine report is a report on the run-in period.

12   There were 19 deaths on ethmozine and only one in the

13   treated group.

14   And I would say based on the carvatelol

15   experience the right way to do a run-in period like

16   that where there's any chance of people dying during

17   the run-in period is to have a control group for it,

18   and then you can go about your business.

19   I think that would work, although the CAS

20   II is the only case that I know where anybody's done

21   it, but you pay a tremendous price if, say, a third of

22   your patients aren't going to tolerate the drug and

1   you just randomize from day one. You know, a third of

2   your patients don't make it through a week, and you

3   get a funny answer.

4   So it's worth thinking about how to do it

5   in a way that's interpretable. Most mortality studies

6   don't need a run-in period. You don't have to be sure

7   anything's stable. You don't have to be sure they

8   have the disease. You already know that.

9   It's only when you're trying to screen for

10 people who can't respond to it that it becomes an

11 issue, and the thought of randomizing the run-in

12 should be considered.

13   DR. THADANI: How long a run-in? Could it

14 be just patient tolerance dose one? Why do you need

15 weeks? I mean in a mortality study all you want to

16 know is patient doesn't collapse on you because you

17 want to know the side effects of the drug. So why

18 can't you say maybe four, five, six days rather than

19 weeks?

20   DR. FISHER: No, I agree. If the adverse

21 reaction is almost invariably present immediately,

22 then the total exposure may be such that -- I mean,

1   you can estimate the expected number of deaths if

2   things are going well, and in that case you could

3   probably put everybody into an open label, quick

4   evaluation.

5   DR. THADANI: If I may ask one short

6   question, what happens in the trial which is ongoing

7   and your have the study on the basis of the current

8   concomitant therapy, and then down the road a drug

9   comes which saves lives?   Beta blocker would be the

10   example at the present time.

11   Then the physician runs into a dilemma

12   who's running the trial. The patients want it.   If

13   you don't do it, my colleague is going to put them on

14   the drug, and then what happens?   The trial is null

15   and void or you hope the user of the new drug is going

16   to be the same in both patient populations, the

17   placebo and other group, and how do you handle that?

18   I realize it isn't concomitant, but

19   concomitant has changed when the trial is halfway

20   through and not over, and what are you going to do?

21   Analyze the data and other factors are going to be in

22   the new drug or the drug being tested?

1   DR. FISHER: Yeah, this, of course, isn't

2   so much study design because you knew this was going

3   to happen, you would have prepared for it.   My

4   personal view would be that provided, as far as you

5   can tell from the mechanism, it should be an

6   independent mechanism of action, the new drug you're

7   adding, from what you're already studying, but you

8   would allow introduction because it would actually be

9   useful to have experience if this is going to be a

10   standard concomitant therapy, assuming things work out

11   well.

12   And then, of course, you have to monitor

13   your data very closely, and although it's historical

14   control because there's before the new addition and

15   after the new medication, and then you have a group

16   that didn't change you could try to look at, but you

17   would look to see if something bizarre was going on,

18   but if you couldn't demonstrate something, then I

19   would propose that you would just continue your trial,

20   and although it would have been nice if you had had

21   the foreknowledge that this drug or whatever came in

22   was going to appear and would be approved, everybody

1   would realize what happened, and you would probably

2   still get approval at the end if the trial were

3   positive.

4   CHAIRPERSON PACKER: Lloyd, I just want to

5   again clarify. You've already described your comments

6   on 4.2. As I understand it, you're pretty much okay

7   with 4.3, 4.4, and 4.5, and 4.6. You've already

8   mentioned the comments of the putative placebo in 4.7.

9   DR. FISHER: By the way, the 4.3, 4.5,

10   4.6, which is kind of like motherhood and apple pie --

11   CHAIRPERSON PACKER: Exactly.

12   DR. FISHER: -- I didn't skip it because

13   it's routine. They're very important concepts, and if

14   possible, there should be placebo controls. There

15   should be blinding. There certainly should be

16   randomization.

17   But I don't think, unless anybody on the

18   panel disagrees with that view --

19   CHAIRPERSON PACKER: That's right.

20   DR. FISHER: -- we obviously shouldn't

21   spend time on it.

22   CHAIRPERSON PACKER: In fact, the purpose

1   of doing that is just to simply make sure that

2   everyone has heard that you're okay with those

3   sections. I understand they're a little bit of apple

4   pie and motherhood, but --

5   DR. FISHER: Well, last week I opposed all

6   three, but this week I'm in favor now.

7   CHAIRPERSON PACKER: Okay, good. Okay.

8   Barry.

9   DR. MASSIE: Yeah, I think that this

10 concomitant therapy is clearly the issue that requires

11 more thinking than the others, as Lloyd has brought

12 up.

13   The issue of the new therapy is clearly a

14 critical one. I'm afraid one's stuck with the luck of

15 the draw. There's really no solution to it, but it is

16 important to think and it may be important for the

17 committee at the end of the day to look at the data.

18   But let's say you're giving a drug that

19 slows heart rate and then beta blockers come along and

20 you get much differential introduction of a good drug.

21 That could have a powerful effect in le sening the

22 benefit that might be observed with an effective drug

1   there.

2   The other issue, of course, is it changes

3   the event rate, let's say, and let's say reduces

4   mortality by 30 percent, and your power was already

5   sort of marginal for the anticipated event rate in

6   your population. You probably might want to and, I

7   think, ought to be allowed to resize your trial at

8   that point.

9   DR. FISHER: A lot of trials these days,

10   maybe even the majority, are designed to go for

11   numbers of endpoints actually rather than --

12   DR. MASSIE: Right, but if you have a

13   differential effect on the difference --

14   DR. FISHER: If you have a treatment

15   interaction where it lessens the effect, that's much

16   more difficult, and I don't have any great solution as

17   I sit here. I mean, I'd need to think about that a

18   while as to whether --

19   DR. MASSIE: I don't think that there is.

20   I think if you see it coming, you try to get people on

21   that drug in advance, but since physicians pick up on

22   the use of new drugs pretty slowly, that's not likely

1   to be too effective either.

2   I just think it's sort of the luck of the

3   draw and see what's down the horizon, but I don't see

4   any way that people can look at it -- although if you

5   saw -- I guess what you could say is in your Cox

6   proportional hazards model somewhere along the line,

7   you might include a term that's not just a baseline

8   term, if you have, for instance, five times as many

9   people going in beta blockers with one therapy than

10 another in your randomized trial.

11   CHAIRPERSON PACKER: Yeah, but, Barry,

12 that's hard.

13   DR. MASSIE: I know. It's very hard.

14   CHAIRPERSON PACKER: It's hard to -- can

15 you   put into a Cox model a post randomization

16 variable?

17   DR. FISHER: There is a --

18   DR. MOYE: Well, there's a procedure

19 called a Cox model with a time dependent covariant,

20 which is when a Cox model is used, it's usually used

21 to consider a variable which is measured during

22 follow-up and on which therapy itself might have an

1   impact you can use this time varying covariant.

2   But the use of the model doesn't transform

3   us   out   of   the   problem.   It's   a   difficult

4   interpretation problem nevertheless.

5   DR. FISHER: Yeah, if you have this five-

6   to-one ratio, that means the two groups are clinically

7   distinguishable in some way to start with because they

8   had different profiles, and that's why one group had

9   a, say, beta blocker added so much more, and it could

10   be a fairly devastating thing.

11   Let's say that was in the placebo group

12   and the beta blocker had a beneficial effect so that

13   you lose the overall --

14   CHAIRPERSON PACKER: This is not an

15   irrelevant problem. We are in the midst of an era now

16   in the area of heart failure where we now have trials

17   with   three   different   beta   blockers   showing   a

18   significant and important impact on the natural

19   history of disease, and yet a majority of patients

20   with heart failure are not yet on the beta blocker.

21   In fact, it would be fair to say that a minority of

22   patients are on a beta blocker, but that proportion is

1   likely to change in the next several years and will

2   change during the course of the conduct of a clinical

3   trial.

4   So that maybe it wouldn't be an

5   exaggeration to say that baseline use of beta blockers

6   in an evaluation of a new drug might be ten percent in

7   both groups and might increase to 40 or 50 percent

8   over the course of two or three years.

9   That may or may not be a problem depending

10   on whether there is an interaction between beta

11   blockade and a new drug or whether beta blockade would

12   reduce the magnitude of the effect or the dose

13   response relationships of the drug and would be

14   particularly problematic if the utilization of beta

15   blockade post randomization was not similar in the two

16   groups, which could occur either because the actual

17   drug being studied has an effect on heart rate or

18   because of some other physiologic basis for an

19   interaction.

20   It actually is a particularly relevant

21   question at this time because it influences the design

22   of every trial which is now ongoing.

1   Now, this is not a unique period of time.

2   We encountered it exactly at a similar time when ACE

3   inhibitors became more widespread, but we are

4   encountering that era now, that transition era now,

5   and as far as I know, there really isn't any solution.

6   When Lem was speaking, I saw both Tom and

7   Dave shake their heads both this way and this way at

8   various points in the conversation. It probably would

9   be important to hear briefly what each of them have to

10   say about this issue because it is such a relevant

11   issue in this era.

12   DR. MASSIE: Just to frame it for a

13   second, the effect of beta blockers looks like it's

14   panning out that from meta analysis, which is an

15   effect on mortality that is greater than I can expect

16   any other drug is going to be seen.

17   Therefore, you're really putting in a

18   major confounding factor. It's not like it's a ten

19   percent reduction. It looks like a 30 percent

20   reduction in mortality, and it will be hard to add on

21   in a group that's on it already, and it might be that

22   any drug we're studying wouldn't have an effect a size

1   that big. So if there's differential use, it just

2   would cloud the issue.

3   So if Lem had a solution there, it would

4   be nice to hear it.

5   CHAIRPERSON PACKER: Tom and Dave.

6   DR. FLEMING: I come back to a general

7   principle that I find guides my own thought in

8   designing trials. We ought to design trials to

9   address questions that are clinically relevant, i.e.,

10 that address what the efficacy and safety of the

11 intervention is in the real world manner in which it

12 would be applied.

13   Hence, concomitant meds. play a major role

14 here, and I believe should be allowed to be delivered

15 as they would in clinical practice, and as you point

16 out, it may be that clinical practice for standard of

17 care evolves during the course of the trial.

18   I believe we need to let that evolve, and

19 to the extent that it does and we're looking at

20 baseline evolution, the randomization is largely going

21 to maintain comparability between these two groups,

22 and what I heard Bob saying at one point is that you

1 can stratify based on baseline covariants, and all of

2 that is fully appropriate and fully interpretable.

3 Lem was talking about what happens though

4 when you look at adjusting for exposure to

5 interventions, not imbalances at baseline, but

6 involved during the course of the study, and we were

7 shaking I heads, I think, in concurrence with Lem

8 actually that such analyses can be done, but are

9 extremely difficult to interpret.

10 Specifically, in my view, if there are

11 imbalances in concomitant meds. after the time of

12 randomization, that could well be the effect of the

13 intervention or could be carrying part of the

14 treatment signal. Any time varying covariant could be

15 carrying treatment signal, and hence the

16 interpretation of an analysis after adjusting for a

17 time varying covariant is problematic.

18 So basically one needs to distinguish

19 between imbalances at baseline versus imbalances that

20 evolve during the course of the intervention, and I

21 would advocate very much that we allow concomitant

22 meds. to be delivered as they would in the real world,

1   to evolve if evolving practice evolves.

2   All of that can be readily adjusted for

3   and interpreted based on their baseline differences,

4   but differences that evolve over the course of the

5   intervention after randomization could well reflect

6   treatment effect and largely shouldn't be adjusted out

7   based on time varying covariants.

8   CHAIRPERSON PACKER: Dave.

9   DR. DeMETS: Yeah, I would agree with what

10   Tom said and support what Lem was getting to, I think.

11   There is a tendency to believe that the tools that we

12   have available in statistics can sometimes rescue us

13   from these dilemmas, but I don't think that's true in

14   this case.

15   There are examples in looking at

16   compliance in general to therapies, and if you sort of

17   analyze data by how people comply to the therapy you

18   prescribe, you know, you can get nonsense results,

19   placebo compliers doing better than non-placebo

20   compliers, that kind of thing, and the same issues are

21   true for concomitant meds.

22   It's a dilemma, and it's a nasty one, but

1   statistical methods, even though sophisticated and

2   sexy as they may sound, won't rescue us from this

3   fundamental problem unfortunately.

4   DR. FISHER: Just one design point though.

5   I think the best procedure when something comes up

6   would actually be get the investigators together and

7   say, "Let's try and put everybody on beta blockers,"

8   if you agree that's to be done, rather than just

9   letting things go as it happens to go.

10   DR. RODEN: Why wasn't that done in CAS,

11   Lloyd?

12   DR. THADANI: That's the only way to stop

13   it because as you said, drug is very effective. You

14   almost reach six months left, and suddenly patients on

15   placebo, for example, go on a beta blocker and your

16   mortality becomes narrower. You have killed a drug

17   which is effective.

18   So I think probably not mandated, but I

19   think all of the investigators perhaps, as you say,

20   should be told unless you definitely feel otherwise,

21   contrary indications to known, say, beta blockers --

22   certain counterindications exist -- put everybody on

1   it.

2   Maybe low doses are going to differ. What

3   you do with the dose in the study, you find the dose

4   only which is used in the study is very high dose or

5   X dose which might have a major interaction with the

6   drug you are studying, which is your investigative

7   drug.

8   CHAIRPERSON PACKER: Udho, this is the

9   ideal state where everyone should be on the drug is

10   nonachievable. It's not only a matter of clinical

11   practice. It's also -- it's not only a matter of

12   dose. It's also a matter of during -- the news

13   evolves on a continuous basis. We all have trials of

14   other agents that come around. There's no point in

15   time when there is equilibrium in this field.

16   And not only that, but a determination, a

17   consensus as to what constitutes equilibrium is very

18   elusive, and I don't think this is an achievable

19   state.

20   Bob.

21   DR. TEMPLE: Well, perfection isn't

22   achievable. The problem of the new patients entering

1   the trial having additional drugs is relatively easily

2   solved. You can stratify it if you're worried about

3   it. That's not the problem.

4   But as Tom said, the problem is what's

5   going to happen if people go on therapy in

6   differential rates afterward.

7   There's no reason why if you perceive the

8   community to be heading toward a situation where most

9   people with heart failure are unresponsive to ACE

10   inhibitors and diuretics and are getting beta blockers

11   to do the trial in a population of people that's

12   already on a beta blocker.

13   That doesn't mean the whole world is

14   already on a beta blocker, but that's a reasonable

15   trial population. So that you could do that if you

16   see that's the way it's going and save a lot of

17   trouble, I would say.

18   I have one other point on a different

19   matter. It's not controversial, I guess, but Section

20   4.3 refers to placebos in an ambiguous way and

21   confuses placebo control with a no treatment control,

22   and the last reason for not needing a placebo, that

1   is, the lack of a placebo effect, is wrong.

2   I'm sensitive to that because there have

3   been a number of publications recently that have

4   spoken as if the response in the placebo group is a

5   placebo effect. Well, that's totally naive. That's

6   not what it is at all.

7   It's the effect in the absence of

8   treatment, but it's partly due to placebo. It's

9   partly due to natural history, partly due to all kinds

10   of things.

11   So I think the reason given for number

12   three is not right, and there's a more complicated

13   explanation for when an active control is okay, and it

14   isn't this. So I just want to flag that. I'll send

15   you comments.

16   DR. FISHER: There's another funny

17   sentence in this paragraph which is one reason for not

18   having a placebo is the new drug is known to be

19   superior to another drug that is known to be

20   effective, which sounds as if the drug should already

21   be approved, I mean, if taken literally. So I wasn't

22   sure what was meant there.

1   CHAIRPERSON PACKER: Right. I'm reading

2   it now actually.

3   DR. FISHER: I think it's misphrased.

4   CHAIRPERSON PACKER: I think it's

5   misphrased.

6   DR. TEMPLE: Superiority in an active

7   controlled trial is evidence of effectiveness --

8   CHAIRPERSON PACKER: Yes.

9   DR. TEMPLE: -- unless the active control

10   is thought to be dangerous.

11   CHAIRPERSON PACKER: Right. Number one

12   I thought said -- it may not, in fact say -- that if

13   you beat an active control, that constitutes evidence.

14   DR. FISHER: What I had in my notes was I

15   had circled "no" and then put "shown," question mark.

16   So you're trying to show that.

17   CHAIRPERSON PACKER: Is shown as opposed

18   to know. Yes.

19   Rob?

20   DR. CALIFF: Milton, I have a dilemma here

21   in my relentless pursuit to reduce the cost of these

22   trials. I've heard our statistician friends say that

1   even in a broadly used single category of additional

2   drug, one cannot have any confidence in post

3   randomization analyses of subgroups, and yet as we're

4   trying to do clinical trials in the world, we're

5   having a hard time finding enough available sites

6   because the coordinators are spending hours to days to

7   months tracking down every drug a patient is taking,

8   when it was started, when it was stopped, and if it

9   was done multiple times, every time it happened, at

10   the cost of thousands of dollars per patient,

11   particularly for heart failure trials.

12   If we can't make use of something as broad

13   as half the population on a drug, what are we doing

14   all of this other stuff for, and why is the FDA

15   forcing these drug companies to do this, thereby

16   limiting the number of good studies that we can get

17   done?

18   CHAIRPERSON PACKER: All right. Rob, I'll

19   take the Chairman's prerogative here of suggesting, I

20   guess, three things.

21   One, is it actually not a point for the

22   guidelines because the guidelines actually don't say

1   that concomitant medications need to be registered

2   faithfully, compulsively, and continuously during the

3   course of the study?

4   Second is I think that the requirement for

5   the measurement of concomitant medications may be more

6   conservatively interpreted by the pharmaceutical

7   industry than, in fact, may be required by the agency.

8   And I think that that least to point

9   number three, which is these issues probably need to

10   be discuss a priori as part of a development plan, a

11   point which I think you would agree with. So true?

12   John.

13   DR. DiMARCO: I'm not sure when the right

14   time to bring this topic up is, but since we're

15   talking about concomitant therapy, it struck me as I

16   read the entire guidelines that there's no mention of

17   defibrillators in the entire document.

18   In thinking about it, there's a

19   concomitant therapy which is becoming more and more

20   introduced in patients with heart failure.   I

21   shouldn't say doesn't have effect on heart failure,

22   but certainly can have an effect on hospitalizations,

1   can have a significant effect on mortality, and I

2   could also perceive a drug which might produce

3   symptomatic improvement in heart failure, which would

4   have no harm on mortality in patients with

5   defibrillators and yet significant harm on mortality

6   in patients without defibrillators.

7   Since we're talking about this, I'm

8   curious whether the heart failure mavens and the

9   statisticians would like to address what should be

10   done with defibrillators other than putting them in

11   everybody, which I think may not be a condition for

12   most studies, but is something that will come up

13   during the course of the trials.

14   CHAIRPERSON PACKER: This actually --

15   John, I can speak to the issue in terms of guidelines.

16   Defibrillators here are really treated as any

17   background intervention and any background therapy.

18   If one believes that there might be an interaction

19   between the use of defibrillators, then one could, in

20   fact, stratify for that variable at baseline.

21   However, the continued utilization of

22   defibrillators post randomization is it raises the

1   same complexity as the potential increased utilization

2   of any therapy, including beta blockade, and is very

3   hard to deal with statistically, and if a sponsor, I

4   think, feels that there is an interaction with the use

5   of defibrillators, they could design their trials to

6   either include only such patients or potentially

7   exclude all such patients at baseline.

8   But that would really depend on the

9   specific characteristics of the drug being developed.

10   My view is it's just like any other background drug.

11   DR. DiMARCO: Yeah, except the fact that

12   it will change your event classifications as well

13   because you have to decide what you're going to do

14   with defibrillator discharge.

15   CHAIRPERSON PACKER: That's true, but

16   remember we also deal -- and we're going to be getting

17   into this -- as to what constitutes an endpoint in

18   trials, and whether cost specific classifications are

19   valuable, which is pertinent to the issue that you're

20   bringing up, and I think also whether there are events

21   that are similar to death, but are not death, and

22   defibrillator   discharge   is   one   possibility.

1   Transplantation is another; LVAD insertion.

2   I don't want to even limit the discussion

3   as to what, in fact, may constitute a reasonable

4   endpoint, but we actually are going to talk about that

5   specifically in a short period of time.

6   We're going to go -- oh, I'm sorry. All

7   right. We're going to go one final round, which will

8   be Bert, Tom, Rob, and we'll go on to the next

9   subject.

10   PARTICIPANT: Final round on all of

11   Section 4?

12   CHAIRPERSON PACKER: It's all on Section

13   4.

14   DR. PITT: One thing that isn't addressed

15   in the document, Milton, is the other guidelines for

16   the evaluation of a drug in a class that has been

17   shown to be effective. What is the FDA going to

18   demand?

19   There hasn't been class labeling, and I'm

20   not advocating there should be, but how does the

21   sponsor go about -- what should be the hurdles to

22   overcome in that situation? And somewhere in the

1   document it would be nice to address that.

2   CHAIRPERSON PACKER: Actually, Bert, the

3   absence of that discussion was, in fact, intentional.

4   First of all, it's a guideline which doesn't

5   necessarily cover everything.

6   That discussion is a difficult one. My

7   sense, it might very well depend on the very specific

8   characteristics of the agent being developed, how

9   persuasive the data might be for the class, whether

10 there are alternatives.

11 For example, would you put an A2

12 antagonist in the same, quote, class as an ACE

13 inhibitor? And you could argue, you know, both ways.

14 And it's not only an issue with respect to

15 efficacy. It's an issue with respect to how much

16 safety data do you need and would you need less safety

17 data if it was in the same class even though it's a

18 different chemical, and it's really, really

19 complicated.

20 DR. PITT: The reason I bring it up,

21 obviously you can't do placebo controlled trials for

22 the next X ACE inhibitor or the X beta blocker, and we

1   talked about here positive control trials and said,

2   boy, we don't like that, but we have to address it

3   somewhere because that's a practical problem with many

4   different agents.

5   CHAIRPERSON PACKER: Although I would say

6   that I remember a discussion years ago at this

7   committee when a sponsor came in asking for a claim

8   for a calcium channel blocker for vasospastic angina,

9   and the claim was primarily based on the fact that it

10   was every reason to think the drug would work for

11   vasospastic angina, but they couldn't find anyone not

12   treated with a calcium channel blocker to enroll in

13   their trials and, therefore, wanted a claim based on

14   the mechanism.

15   And they had tried to find the patients.

16   They tried to do the trial and couldn't find anyone,

17   and I think our response to them was I think God is

18   trying to tell you something.   Sometimes you don't

19   need to develop a drug.

20   (Laughter.)

21   CHAIRPERSON PACKER: Tom.

22   DR. FLEMING: I'd like to address a few

1   points, separate points. The first is in response to

2   Rob's comment about do we need to collect concomitant

3   meds. that are initiated after time of randomization

4   or baseline.

5   I don't think the comments that some of us

6   were making before was that that information isn't

7   relevant, although I think Rob's making a good point.

8   Maybe we don't need to collect as much data as we do.

9   Nevertheless this data can still be relevant.

10   Our   concern   was   using   this   in   time

11   dependent covariant models as part of your primary

12   analysis and the reservations with that. This type of

13   information is still certainly informative, and in

14   some   settings   if   those   concomitant   meds.   are

15   particularly toxic, expensive, or inconvenient, it's

16   part of the treatment effect or part of the efficacy

17   outcome, for example, as you would see in a lupus

18   trial looking at Agent A versus standard of care where

19   concomitant meds. are prednisone.

20   This type of information certainly can be

21   very informative in the overall assessment of impact

22   of an intervention.   Concern was using it as time

1   varying covariants.

2   I'd like to quickly touch on three other

3   issues that we have discussed briefly to mention a

4   couple of important specifics, I think.

5   Section 4.4, the need for blinding.   I

6   think we've heard strong endorsement of this need.   I

7   certainly concur in general with that, although would

8   want to be sure that there is a caution that the

9   placebo needs to be inert.

10   I've seen trials where the placebo wasn't

11   inert, was actually providing some of the benefit, and

12   in one setting providing some harm.   A real quick

13   illustration of that was a study that Dave and I were

14   monitoring a number of years ago that was looking at

15   adding Agent A or Agent B to standard of care, a

16   three-arm study, and they wanted to avoid giving two

17   thirds of o the people the A placebo and two thirds of

18   the people the B placebo.   So A and B were allocated

19   open label, and then two thirds of the A were given

20   active A, one third placebo; two thirds of the B given

21   active B, one third placebo in blinded ways.

22   So we actually had three groups, one of

1   the groups, the placebo group, half of whom got A

2   placebo, half of whom got B placebo randomly. So we

3   actually have a rare case of evaluating whether the

4   placebos were inert.

5   At the interim analysis there were 19

6   deaths in the placebo group, 17 on A placebo, two on

7   B placebo. So in one of these rare cases where we

8   could evaluate efficacy or inefficacy, inertness of

9   placebo, we saw striking differences.

10   So I would hope that when we go to

11   placebos that we do so with an awareness that the

12   inertness of the placebo is a critically important

13   condition for the interpretability of the trial.

14   A second point, use of positive control,

15   Section 4.7, I think does give important cautionary

16   statements about the use of positive controls and

17   ultimately making conclusions about efficacy, but I

18   think it may be overly cautionary in the sense that

19   there are settings in which an establishment of

20   equivalence could allow for a conclusion of efficacy

21   of an intervention.

22   I would argue that there are three key

1   conditions, and the first is that the active control

2   needs to be one that is known to be very effective;

3   secondly, with a precisely defined level of efficacy;

4   and, thirdly, with that being precisely defined in the

5   setting in which this trial will be conducted.

6   If you have such an active control and you

7   are then able to establish equivalence of a new

8   therapy against that active control, I believe that

9   does allow you to conclude according to a reasonable

10   standard for strength of evidence that you have

11   efficacy, and this could be well motivated in the

12   setting where your new intervention has a profile that

13   would provide improved toxicity, improved convenience,

14   or improved cost relative to standard of care.

15   The final point is relating to the 4.9 on

16   use of open label run-in periods. I think we've heard

17   that these can be very helpful in focusing a

18   population into those who are tolerant and compliant.

19   We've also heard about the clever design in CAS II,

20   which I strongly endorse if you're going to use this,

21   which is the randomized control during the run-in to

22   be able to assess for possible adverse effects during

1   run-in.

2   There are some other issues though with

3   this design that at least should be acknowledged, at

4   least qualifications, if not limitations, and the

5   first is that such a design limits labeling, possibly

6   appropriately, to those people who are compliant and

7   tolerant. Those are the ones that are assessed in the

8   trial.

9   And, secondly, that the design is really

10   assessing whether you continue versus stop as opposed

11   to whether you treat versus don't treat because

12   everybody is getting the run-in, and then you

13   randomize to treatment versus control. You're really

14   assessing continuation of therapy versus stopping of

15   the therapy.

16   And if you happen to have a setting where

17   you have withdrawal toxicities or adverse events

18   associated with stopping, the differences that you may

19   see may not be attributable to benefit from

20   continuing, but rather adverse effects from stopping.

21   DR. RODEN: When I read this over, I

22   wasn't sure whether the last sentence of Chapter 4

1   said what it was supposed to say. Is that what you

2   meant to say?

3   CHAIRPERSON PACKER: The one that begins

4   "open label"?

5   DR. RODEN: Right, right. I would have

6   actually, based on all of the arguments you've

7   presented, I would have thought it should say the

8   opposite, or am I just misinterpreting it?

9   CHAIRPERSON PACKER: No, I think several

10   sections of this document have been discussed in

11   various meetings. This happens to be one paragraph

12   that this is the last paragraph. This is Lines 478 to

13   482.

14   This is a paragraph that actually has been

15   extensively discussed in the past, and the statement,

16   the second sentence of that, actually reflected the

17   feelings of those who were at the meeting, that they

18   felt that it was -- that there is a potential problem

19   with the exclusion of all of these patients in

20   general, and this has all been mentioned; that the

21   concept of identifying responders and treating all

22   responders caused people a little bit more discomfort

1   than excluding patients who had an adverse effect

2   because they felt that in clinical practice it would

3   be natural to exclude patients who had an adverse

4   effect.

5   Having said that, Rob has made the point

6   on this issue that the exclusion of such patients

7   needs to be considered very, very carefully because by

8   excluding those patients from analysis, one is

9   cleansing the database in a way that, one, a physician

10   who would treat a patient in clinical practice

11   wouldn't necessarily know what to expect from the next

12   patient they were planning to treat, but that is

13   inherent in the issue of an open label run-in period.

14   DR. CALIFF: I think both Tom and Bert

15   raised the issue. I'm disappointed that we've really

16   avoided the positive control issue and acted like it's

17   not something that really needs to be dealt with in

18   this document because there is a place, substantial

19   place and increasingly so, for therapies which do much

20   of the same as available in proven therapies, but have

21   a better side effect profile or are cheaper to make or

22   have some other advantage and not only in heart

failure, but most other areas of therapy.

Pretending that you can do a placebo control trial ethically is just a sham. It's not reasonable. So to say, "Don't do active control trials. We can never be sure about them," leaves who areas of therapeutic development unaddressed and potentially at risk.

CHAIRPERSON PACKER: While you're raising this, let me, if I could -- and, Bob, I want to sort of introduce the topic and then open it up -- let's assume that one met the criteria that Tom has put forward, and let me, at the risk of oversimplification, as I understand the terms, that the active control selected for a positive control trial must be effective; that the degree to which it's effectively must be precisely determined; and that the trial being proposed should be similar in clinical setting to the trials in which the active positive control had been established to be effective.

I think those are the three criteria, Tom?

DR. FLEMING: Yes, that precise at the level of efficacy has to be attributable to the

1   setting in which the study is going to be conducted.

2   CHAIRPERSON PACKER: Right. The

3   difficulty one frequently has in heart failure is not

4   the first or the third, but the second, and that is

5   the precision with which one can define a treatment

6   effect is somewhat problematic, and the difficulty

7   that is encountered in the positive trial is to what

8   degree do two treatments need to be demonstrated to be

9   equivalent, and what is meant by equivalence.

10   In other words, how much uncertainty are

11   you willing to accept that a treatment might be

12   inferior to a specific degree in exchange for the fact

13   that the treatment might be cheaper or safer?

14   Bob?

15   DR. TEMPLE: Well, this is a very

16   complicated question. What you, in fact, have to be

17   sure of is not precisely what the effect of the active

18   control is, but that it is at least a certain size,

19   which you then set as your margin, and what you try to

20   show is that the new drug is not to a reasonable

21   confidence interval worse than that.

22   That assures you that the new drug has

some, any effect more than placebo. Now, usually when

that comes to a committee like this, there's a shriek

of horror. What do you mean? I'd be giving up 50

percent, 60 percent of my effectiveness?

Of course, when you have shown that a drug

is more effective than placebo at .05, we naturally

assume the point estimate is the size of the effect,

but that's wrong. All we're really sure of is that

it's better than nothing.

So in practice when these issues come

before this committee, in fact, as they did for

thrombolitics, we were able to say with fair

confidence that we knew the effect was at least a

certain size, and there was a lot of controversy about

how to do that. Do you take the worst result ever

seen? Do you pool all of the data and take the lower

bound? In the 95 percent confidence interval there's

no rules on this and not much experience either, but

you do it somehow.

And in that case the committee was unhappy

with setting a margin that would preserve at least 50

percent of it, but it turns out that to try to be sure

that you've preserved at least, say, 75 percent of the

effect gets you into studies in the 40 to 50,000

person range. So it's an extremely difficult problem.

In heart failure, I would predict it's

worse, way worse, because the background therapies

change so much you have very little way of saying what

the effectiveness of any given drug is, and it's a

really serious problem, and sometimes the answer is

like what I guess it was Lloyd said. Maybe the world

is telling you something. Maybe the drugs are good

enough so that it's very hard to study them anymore.

The alternatives include studying a group

that hasn't been studied yet, if you can still find

one, and things like that, but equivalent studies or

noninferiority studies are extremely difficult unless

there's a lot of data.

But in those cases where there is or there

are, then you can design the trials, but it's not

simple, and my answer to Rob is, you know, wishing

doesn't make it so. You might want to know whether

you can do just as well, but you also don't want to

give up effectiveness. You want to have a trial that

1   substitute or actively replace therapies, we end up

2   with this sort of Tower of Babel out there, people

3   advertising their individual drugs and no one knowing

4   what to do and are combining things in ways that could

5   be very unsafe.

6   CHAIRPERSON PACKER: Lloyd.

7   DR. FISHER: I just would like to remind

8   the committee of two things. One is, of course, you

9   just spent half a day, I think it was, on the issue

10   not very long ago, and Bob Finishol gave a large talk,

11   for example.

12   Secondly, when I presented the comparison

13   with placebo data for clopidadril, which to my mind

14   was just incredibly overwhelming mainly because

15   aspirin had been so extensively studied against

16   placebo, and there was this P like ten to the minus

17   11, and this committee had trouble with the approval.

18   I think it's not unfair to say that it

19   took a bit of education by the FDA staff to the

20   committee before the committee began to understand

21   things.

22   So I'm not sure what this committee would

1   do with it, but at least at that time I felt the

2   committee had trouble mentally adjusting to the

3   positive control and was focusing on the P value

4   versus the -- the new drug versus the active control

5   rather than seeing what would have happened had there

6   been a placebo, where to my mind that was a slam dunk.

7   I mean, there was a lot of room for debate

8   about how it did versus the active control, and if

9   this committee is typical, and it's my biased opinion

10   that this committee is one of the best committees

11   within the FDA committee structure; if this committee

12   has trouble, I hesitate to think what might happen

13   with some of the other committees.

14   CHAIRPERSON PACKER: Lloyd, the example

15   that you cited is a good one because, in fact, that

16   was an example in which I think this committee, the

17   Advisory Committee, for meeting for clopidril, in

18   fact, consisted to a certain degrees of an educational

19   process as to what the concept of a putative placebo

20   was and how one could reach conclusions based on

21   whether a drug worked, in fact, when a placebo

22   controlled trial had not been specifically carried

out, but that the active control had been extensively evaluated and was deemed to be unequivocally effective.

But, in fact, that educational process was carried out in a relatively short period of time, and the committee, in fact, reached the unanimous consensus at the end of the day that they were persuaded by the data that was shown.

So I guess this is a brief, or perhaps not so brief, way of saying that I think we are all educable.

(Laughter.)

CHAIRPERSON PACKER: Jay.

DR. COHN: Yeah, I wanted to come back to the run-in issue again because I've been sitting here trying to think of an appropriate early efficacy endpoint that could allow one to then continue therapy in the responding patient population.

And the document sort of suggests that that's not a very good thing to do, but it strikes me that we may not yet have such early efficacy markers. I guess Rob would call them surrogates, but we may

1   eventually have them.

2   To me it's a very appropriate way to

3   administer drugs. That is, whether it was a blood

4   pressure or a heart rate or a cholesterol reduction or

5   something more sophisticated than that that would

6   identify the responding patient population that would

7   then be eligible for maintaining therapy for long term

8   benefit, it seems to me that's a very appropriate

9   strategy for drug development.

10   We know these diseases are heterogeneous.

11   Everyone is not going to respond, and to insist then

12   that we have to study the strategy to use a drug

13   rather than to target the drug for the patient

14   population that appropriately responds, I think, is

15   again playing as if we're ignorant, and we should be

16   smarter than that, and we should get more smart.

17   So it seems to me that we should leave

18   that as a very open strategy, that if one can find a

19   marker that could identify via responding population

20   that it would be appropriate to do that study, and

21   then the labeling, of course, would have to reflect

22   that exact use.

1   CHAIRPERSON PACKER: Lloyd.

2   DR. FISHER: Yeah.   Just the sort of

3   problem you can run into, Jay, is let's say you're in

4   Class 2 and 3 and you have a moderately long run-in.

5   If you have many deaths, even if you randomize and

6   have a control, you don't have enough deaths in

7   general to pin things down incredibly well.

8   So let's say you appear to have even a

9   beneficial effect in the run-in period, but the P is

10   .6 or something, .8.   So you have a fairly wide

11   confidence interval. If I wanted to argue the case

12   against somebody, I could say, "Well, I'm not going to

13   take the .6, but I'm going to take the upper end of

14   the 95 percent confidence interval to say you might

15   have weeded out people of more risk."

16   So that the people you finally did

17   randomize, in fact, are not a population that would

18   really represent the entire risk of this drug

19   strategy.

20   DR. COHN: Well, I think, you know, it

21   will have to be -- eventual analysis will depend on

22   however the data come out, but if you're only going to

1   treat -- and it depends on how long that run-in period

2   is and it depends on what your endpoint of the trial

3   is.

4   But it strikes me that from a

5   philosophical standpoint, that strategy should be

6   considered to be very appropriate if you can correct

7   for the run-in events itself.

8   DR. FISHER: Right. It depends very much

9   on the -- like one of the things Tom said, that if you

10 eliminate people because they cannot tolerate a drug,

11 it might affect labeling, but to me that doesn't

12 affect labeling at all. I mean the labeling says you

13 should only give the drug to people who tolerate it?

14 That's no big limitation because that's what happens

15 when you actually give the drug.

16   But the events during this period, I think

17 are something that we need to sort out better, how

18 we're going to handle it, what we expect to see.

19   DR. COHN: Right, and I think, you know,

20 the role of the regulatory body is obviously to try to

21 come as close to the decisions that relate to

22 practice, and of course, practice does not give drugs

1   to people who don't respond or who have adverse

2   effects.

3   So trying to link practice with drug

4   approval is obviously positive.

5   CHAIRPERSON PACKER: Tom and then Rob.

6   DR. FLEMING: If everything was black and

7   white, Lloyd, I would agree. If it were totally

8   compliance or totally tolerant versus not at all,

9   sure, it's not a limitation, but there are varying

10   degrees, and there are many illustrations where

11   someone my be partially tolerant, i.e., being able to

12   take a number of courses of the intervention and

13   benefit from that.

14   Jay's comment is reminiscent to me of what

15   I see happening in HIV/AIDS setting with viral load,

16   i.e., you have a mechanism; you have a marker. People

17   in that setting are referring to strategies for using

18   interventions to achieve an effect on a marker, i.e.,

19   you dose until you achieve in HIV/AIDS two log

20   reduction in viral load.

21   That's certainly a very rational way to

22   specify how you might strategically use an agent. You

1   would need to evaluate that strategy though, and you

2   would have to evaluate that strategy by randomizing

3   people to a strategy that dosed until you saw an

4   effect on the marker, and what impact does that

5   strategy have on a clinical outcome versus not using

6   the agent at all or against a strategy of using the

7   agent without being driven by effects on the marker.

8   And, in fact, that's what's happening in

9   a number of HIV/AIDS trials. So what you're talking

10   about is clinically a rational approach. It creates

11   a different regimen, so to speak, a regimen that's a

12   strategy for delivery of an intervention that's driven

13   by whether you achieve the intended effects on a

14   marker.

15   You still have to look at a randomized

16   assessment of that strategy on clinical endpoints.

17   CHAIRPERSON PACKER: Rob.

18   DR. CALIFF: I think Tom said it well, but

19   I do want to respond to Jay's comments that we

20   clinicians don't treat patients who have adverse

21   effects.

22   Yes, we do. We treat them until they have

1   an adverse effect, and then we stop, and if we haven't

2   quantified what the risk is of an adverse effect in

3   the intended population to treat, then I would submit

4   we really don't know what we're doing.

5   Tom's approach would deal with it, that

6   is, randomize to the strategy of treating until you

7   have an adverse effect and stopping. That obviously

8   increases the sample size substantially and creates a

9   difficulty in that arena.

10   So we all agree it's a tough problem. I'm

11   not saying I know the answer, but the statement on

12   face actually I disagree with. We do treat people

13   until they have an adverse effect.

14   CHAIRPERSON PACKER: Yeah, I think the

15   situation is actually more complicated, and it gets

16   back to a discussion that we had at the very beginning

17   of the day in terms of whether labeling actually

18   reflects clinical use because, Ray, correct me if I'm

19   wrong. It wasn't that long ago when this committee

20   would see trials of anti-angina drugs. We don't see

21   that very often, but we used to actually see a fair

22   number of trials of pharmacological agents for the

1   treatment of angina.

2   And it wasn't that unusual for patients to

3   be randomized in their trial based on their response

4   to an initial administration of the drug during a run-

5   in period, for example, some of the nitrate trials, a

6   lot of the nitrate trials.

7   And, in fact, in the existing document,

8   anti-anginal guidelines -- I understand it's ten years

9   old -- would, in fact, encourage the use of open label

10   run-in periods where patients would be exercised

11   before and after a sublingual nitroglycerine and be

12   randomized only if they had a certain increase in

13   exercise time after a sublingual nitroglycerine.

14   That was felt to be very good design

15   because it enriched the patient population and

16   certainly would be consistent with Jay's emphasis on

17   mechanisms. You know, you were finding the mechanism

18   by respond to the drug.

19   On the other hand, in clinical practice no

20   one does that. Not a single physician in clinical

21   practice ever decides whether to give nitrates or not

22   based on a patient's response to sublingual

1 nitroglycerine.

2   DR. LIPICKY: Well, there are some minor

3 subtle differences here that might be worth talking

4 about. In fact, physicians and patients do that with

5 nitrates. If it doesn't work, they don't take it.

6   CHAIRPERSON PACKER: Really?

7   DR. LIPICKY: Yeah.

8   DR. THADANI: Ray, that's not true.

9   DR. LIPICKY: I mean, you know, if they

10 get no relief of their angina, they're not going to

11 pop another sublingual nitro.

12   DR. THADANI: That's not true.

13   CHAIRPERSON PACKER: I don't thinks that's

14 true.

15   DR. LIPICKY: Well, fine, but nonetheless,

16 part of the reason for --

17   (Laughter.)

18   DR. LIPICKY: -- part of the reason for

19 the enrichment trial, if you would, would be that's

20 reasonably applicable to patients, to drug therapies

21 where there are titrated regimens and where the

22 measurement that you need to make is immediate.

That is, you know, you can tell if blood

pressure goes down. You can tell if people get their

angina relief, et cetera, et cetera. You have the

ability to change dose, increase it or decrease it,

and it's reasonable to say you ought to be able to

tell if this drug works for your patient.

So you do the trial in the population in

whom you're not getting a lot of bad answers because

the drug doesn't work.

That's a totally inapplicable circumstance

to whether or not you're dead or alive and to regimens

where there isn't more than one dose and, in fact, you

can't titrate. If people have died, you can't say,

"Geez, I'm sorry. I gave you the wrong dose."

And so consequently that's totally

inapplicable. That conceptualization is totally

inapplicable.

So it's okay some places, and it has

troubles other places.

CHAIRPERSON PACKER: Bob.

DR. TEMPLE: Nothing stops you from

keeping track of how many patients you passed on to

1   the major trial from the lead-in period. In other

2   words, you could say we screen 1,000 people and only

3   ten percent of them were responsive to nitrate. So

4   you take that into account.

5   CHAIRPERSON PACKER: What does labeling

6   say?

7   DR. TEMPLE: Labeling can say that. I

8   wouldn't say it always does, but as an example, if you

9   want to look at the labeling for Viagra, it will tell

10   you that the patients in trials were screened for

11   response to a single dose, and that all of the data

12   you see from the lengthy trials represent only two

13   thirds of the initial population that were put into it

14   because one third never responded to the single dose

15   initial test.

16   So you can do that.

17   CHAIRPERSON   PACKER: Yeah,   but

18   interestingly enough, the response rates that are

19   quoted, for example, for that product are the response

20   rates from the placebo controlled trials uncorrected

21   for the initial screen.

22   DR. TEMPLE: Well, maybe that's what gets

1   out someplace, but in labeling it's accurate.

2   CHAIRPERSON PACKER: I understand.

3   Udho and then Rob.

4   DR. THADANI: I think the nitrate issue is

5   more complicated. All the trials have not done that

6   way. There are trials, larger trials, which have

7   included all comers, and I think you have to include

8   all comers. Otherwise you're selecting population

9   based on your exercise test.

10   And if I remember correctly, the only

11   reason they looked at the responders was to address

12   the issue of tolerance to nitrates because what you

13   want to do is the effect goes away with time, but I

14   think nobody exercises the patient.

15   One thing is that spontaneous angina goes

16   away with sublingual nitroglycerine is not the same

17   that exercise will improve tolerance. There are 20

18   percent who actually get worse on exercise tolerance

19   of nitrates, and yet it is not in the labeling.

20   And when you compare trials, that becomes

21   apples and oranges. So I think one has to dissociate.

22   The question I was going to raise is,

1   again, coming back to placebo. In heart failure

2   trials, there's always add-on therapy, and so I don't

3   know how you can do active controls when your

4   treatment, say, looks exciting, but you know doesn't

5   improve mortality or morbidity. How ethically can you

6   do an active control in a group of patients where a

7   drug has been shown -- and you have no clue. I'm not

8   talking about the same class of drug. I'm talking

9   about a new class of drug which might have potential,

10   but you have no clue it's going to be as effective.

11   Is it ethical you want to do a trial

12   knowing the fact which is already known that patients

13   are living longer, or should we even talk about actual

14   controls in heart failure when all of the trials have

15   been on add-on therapy, one after two to three, to

16   four drugs now?

17   CHAIRPERSON PACKER: Udho, you mean you

18   think it's totally unethical if someone thinks they

19   have a better ACE inhibitor to do a trial against an

20   ACE inhibitor?

21   DR. THADANI: I think in the same class

22   it's fine, but to say for a different class, no, no.

1   If you're talking about low dose, high dose, that's --

2   say you've got two ACE. What you're doing then is

3   you're saying, okay, both treatments are effective.

4   I'm going to show one is better.

5   But say suppose you've got a new class of

6   drug. Are you going to withhold drugs which have been

7   shown to be effective? I think it's a dilemma, and a

8   lot of IRB committees are not going to allow you to

9   withhold drugs which have been approved to save lives.

10   Hospitalization I can live with.

11   CHAIRPERSON PACKER: I don't think we

12   should dwell on this. I guess it would just be fair

13   to say, and I'll just speak personally, that I don't

14   see any problem doing an active control trial against

15   an established drug if everyone who participates

16   thinks that the hypothesis being tested is reasonable,

17   and I don't think there's anything more complicated

18   than that.

19   Rob.

20   DR. CALIFF: I just come back to a couple

21   of things.

22   On Bob's comment, I think Lloyd actually

1   made a very important point which may be worth

2   emphasizing a little bit more in the document about

3   run-ins. You know, if there's a ten percent response

4   rate and those people go forward and do better in a

5   placebo controlled trial, the critical issue and the

6   other 90 percent is really where they had events

7   because if they just got a headache or something,

8   that's fine, but if they dropped over dead or had

9   worsening heart failure, for example, it seems there

10 is an obligation to quantify that somewhat since that

11 is what is going to be the basis for use in clinical

12 practice.

13   And there is this very difficult problem

14 that was alluded to. If the labeling gives the

15 treatment effect in that ten percent, as we go forward

16 in society we've got more good treatments than we can

17 afford to pay for. We're in the era of so-called

18 evidence based medicine. Comparative evidence is

19 usually based on a perception that you're starting

20 with a population in which you intend to treat.

21   So you end up with sort of a better

22 looking scenario than what you would actually get in

1   clinical practice, making it very difficult to make

2   decisions.

3   CHAIRPERSON PACKER: I think we've

4   probably exhausted this.   It's time to take a break.

5   The intent after the break -- break for lunch, yeah --

6   the intent after the break is to discuss Section 5 at

7   length, which is divided into evaluation of clinical

8   status,   evaluation   of   long   term   outcome,   and

9   evaluation and analysis.   We are going to be spending

10   some time on that.

11   We are not going to be discussing safety

12   today, and if we have time, we'll try to summarize

13   some of the approvable indications.

14   But   there   has   not   been   a   lot   of

15   disagreement   on   the   phraseology   the   approvable

16   indications in the past.   So we're going to try to

17   focus primarily on Section 5 when we return.

18   And we will come back at one o'clock and

19   promptly at one.

20   (Whereupon, at 12:08 p.m., the meeting was

21   recessed for lunch, to reconvene at 1:00 p.m., the

22   same day.)

1   <u>AFTERNOON SESSION</u>

2   (1:10 p.m.)

3   CHAIRPERSON PACKER: The next topic for

4   discussion this afternoon, we're going to continue our

5   discussion on the guidelines for heart failure and

6   focus this afternoon's discussion on efficacy

7   endpoints.

8   Before doing so, let me outline, just

9   describe very briefly the concept is to take all of

10   the comments we have received today and to continue a

11   discussion about revising these guidelines to a point

12   where they may become official.

13   The process by which that would occur or

14   the time frame in which that would occur has not been

15   defined, and I think that the present draft at least

16   provides a useful framework for ongoing discussions

17   and, in fact, may be the only written document for a

18   while.

19   So please take this document in the

20   context of the discussions which have occurred today,

21   and if you combine those two, you might have a pretty

22   realistic idea of what the final outcome might look

1   like.

2   The efficacy endpoints are divided into

3   two sections, the evaluation of clinical status and

4   the evaluation of risk of a major event. Paragraph 2

5   under Section 5 summarizes the rationale for such a

6   division, but let me emphasize, having said that,

7   these two may be very much related to each other, and

8   it is somewhat artificial to separate the two.

9   Lloyd?

10   DR. FISHER: I just wanted to mention one

11   point of information I found useful. The Cardio-Renal

12   Advisory Committee minutes now go on the Internet when

13   they get them. So you can go into the FDA. In the

14   context of taking the document with the discussion,

15   that will be available on the Internet.

16   CHAIRPERSON PACKER: And I think that

17   there are plans right now to put this document onto

18   the Internet at some time in the next week, probably

19   as is because it won't be revised in the next week.

20   Okay. Barry Massie is going to lead off

21   the discussion on evaluation of clinical status.

22   DR. MASSIE: Well, I'm going to try to be

172

brief, although I think I may stimulate longer

discussion later.

Milton asked me to talk about the

symptomatic endpoints, and contrary to some people's

believe, symptoms still do count, I think, in the

process of approving drugs for heart failure. So they

still can serve, I think, as the primary evidence of

efficacy, but they must be clinically meaningful, that

is, something a patient feels, at least as judged by

the patient or perhaps by the physician.

Physical signs and physiologic surrogates

in the current document and particularly hemodynamics,

for instance, as a physiologic surrogate are not

probably in themselves sufficient for approval.

Now, I did want to bring up one point that

in reading through the document I couldn't identify,

which is whether or not these guidelines applied to

diuretics for the use of heart failure. Perhaps we

can discuss that later because there I think physical

signs, if one includes weight and other signs of

volume retention, might serve as a primary endpoint

for approval of a diuretic in the management of heart

1 failure, although that might be labeled a different

2 indication.

3   They should be measured over at least a

4 reasonable period of time. The current document says

5 six to 48 hours for IV drugs. I would believe that

6 six hours is probably a little bit short for some of

7 our drugs, but clearly over a matter of hours to days,

8 and six to 12 months for symptomatic types of

9 endpoints with chronic oral drugs.

10   Now, having said one could likely get

11 approved by showing consistent improvement in

12 symptoms, I think it's also clear in this document

13 that you at least need some estimate of the effect of

14 morbidity and mortality, as well, for long term

15 therapy and probably even for short term therapy,

16 although a different type of estimate.

17   Now, there are basically two types of

18 symptomatic endpoints now, and this is my own

19 categorization. There are symptomatic endpoints as

20 the patient tells you about them, and the symptom

21 scores have been used, various types, visual analogue

22 scores, rating from one to whatever.   Most of the

1 symptomatic scores focus on symptoms related to

2 dyspnea with some level of activity.

3 And then the global assessment of change,

4 which is basically compared to baseline how does one

5 feel on usually a scale of one to five or one to

6 seven.

7 It's important in using these, I think,

8 several points. All of these symptoms actually are

9 usually measured by multiple ways in the same

10 protocol. So there's a real multiplicity problem

11 here, and therefore, I think that one needs to really

12 pre-specify the critical measures. Otherwise you can

13 have five different scales. Unless you know which one

14 is going to count, I think one enters into a morass.

15 The other issue is, of course, the

16 investigators can easily influence the patients on how

17 they feel, and that needs to be avoided if at all

18 possible.

19 And then there's the investigator

20 determined endpoints. New York Heart Association

21 class is often thought to be basically a symptom

22 determined classification that is relatively

objective. I think it's far from that, but not a bad way to assess heart failure as it turns out, looking at the results over studies.

But I think all of us who have read down New York Heart Association class are aware of changes in creatinine, changes in exercise measurements, and deal with more than just what the patients volunteers.

And global assessment of change also would probably be a multi-determined function, not just symptoms, but if the physician is performing at all he knows about the patient.

This raises the two problems I've listed at the bottom. In rating it you shouldn't be influenced by recognizable drug effects. For instance, a beta blocker that drops the heart rate by 15 points might even be something that we considered good, and that might make us feel better and say the patient is doing better globally.

If it's not something we necessarily feel is good, it still might allow us to recognize a drug effect that we think is good. So that type of bias is there, and therefore, it makes mention of an

1   independent assessor.

2   The problem is if you use an independent

3   assessor, you also lose all of this ancillary data

4   which I think has value that we would enter into our

5   New York Heart Association class and our global

6   assessment.   I think that an independent assessor

7   should be avoided if at all possible.   I think it

8   makes a complicated evaluation.

9   Now, other types of symptomatic endpoints

10   are really two others.   Exercise tolerance, which I

11   guess has been our oldest standard for improving

12   symptoms of heart failure since the modern improvement

13   goes, and I think although it's been discouraged and

14   the document gives lots of cautions about the problems

15   with exercise tolerance, a consistent improvement in

16   exercise tolerance could certainly serve as the

17   primary basis of approval, given the other evidence we

18   need about safety, and so on.

19   They can be measured in many ways.   The

20   document, I think, carefully avoids trying to tell

21   people how to measure because we really still don't

22   know.

1   I think it's a problem because it's

2 variable for sure, and because we know that it doesn't

3 necessarily capture drug benefit. Even drugs that

4 improve symptoms may not improve exercise tolerance,

5 and the flip side has been that some drugs that

6 improve exercise tolerance have other adverse effects.

7   Nonetheless, I think it is a way to

8 approach demonstrating improvement in symptoms.

9   Quality of life, I think, is also

10 problematic in part because of the multiplicity issue

11 that comes up very frequently. Hardly anybody will

12 agree on one way to measure quality of life. So there

13 are many scales.

14   I'm involved in one study now where they

15 have four because they can't decide which one to

16 eliminate. One may turn out positive, but then how

17 will one interpret it?

18   So certainly you have to have a very

19 careful analytic plan worked out, and my own bias is

20 that these measurements may not actually measure drug

21 effect or harm in a heart failure specific manner, and

22 my own bias is that this should not serve as a primary

1   measure for approval.

2   And lastly, the composite endpoint, which

3   clearly is sort of a favorite approach in this

4   document, and it's probably a good approach because

5   everybody counts, and it mixes together the major

6   types of endpoints that we look for in a morbidity and

7   mortality study, but while at the same time assessing

8   symptomatic measures in the other patients.

9   However, it doesn't get away from any of

10   the problems with those individuals' symptomatic

11   measurements, and I think we would fool ourselves if

12   we think that this turns out to be, you know, the

13   eureka for how to do it.

14   I think classification remains difficult,

15   and what I think is most difficult in many of these

16   trials, although if you declare the time when you're

17   going to measure it, you can do that, is that time

18   dependance is a very important factor.

19   Many patients, I would say most patients,

20   feel worse and better in the same trial compared to

21   baseline at some point. So you could arbitrarily say

22   three months or six months is the time you're going to

1   measure it, but that might not tell you whether the

2   drug is working or not.

3   And associated with the patient feeling up

4   and down at various times is that there are therapy

5   changes. Maybe they get worse. They get a better

6   therapy added on. Then they feel better, and what are

7   you measuring? We already talked about that, I think,

8   in terms of morbidity and mortality studies, but it is

9   equally true for symptoms.

10   So we really haven't defined, I think, the

11   perfect way to look at symptoms, but I think that at

12   least with drugs that have across the board positive

13   effects that some of these do improve, and it seems

14   like the more subjective they are, asking the patient

15   whether they're feeling better or not seems to be the

16   moist powerful discriminate between a drug that we

17   know works by other measures and one that doesn't.

18   CHAIRPERSON PACKER: Barry, thank you very

19   much.

20   Let me just clarify one thing. In the

21   document that Barry referred to, the concept of an

22   independent assessor is mentioned in the document, was

1   not mentioned, by the way, in any old versions of this

2   document.

3   Entirely, and the document makes this

4   clear, if in order to avoid the concept of

5   confounding, in other words, drugs may produce toxic

6   effects or whatever, and if that's the case, then the

7   independent assessor might help to solve the problem.

8   The creation of an independent assessor,

9   however, creates problems because by the very nature.

10   Because it divorces the assessor from the usual

11   interactions with the patient, it actually may be a

12   more sterilized approach because usually the

13   interaction with the physician and patient occurs at

14   so many different levels, including a nonverbal level,

15   that, you know, an independent assessor, in fact, may

16   not get the New York Heart class or the global

17   assessment quite right.

18   I think you're referring to that, but

19   then, again, if there's some toxic or confounding

20   influence, it may be the only way to do it or maybe

21   they could do it both ways. It would get complicated.

22   Ileana.

1   DR. PINA: Yeah, I want to echo what Barry

2   said about trying to find some kind of composite

3   score. I think when symptoms become difficult to

4   measure that we must look for consistency, and if the

5   majority of symptoms are on the improvement side and

6   one isn't, then we may want to add some weight to some

7   symptoms versus others, but I think that consistency

8   may be more important than just taking one assessment

9   alone.

10   And I agree that the New York Heart

11   Association, the way it's defined is not really the

12   way it's used, and I think when we give someone an

13   NYHA, we really put together everything, including the

14   creatinine and how much they can walk and how much

15   they can do.

16   CHAIRPERSON PACKER: Marv.

17   DR. KONSTAM: I agree with just about

18   everything Barry said, except I'd like to propose

19   reframing it actually, and I've talked about this

20   before, and that is to say that aside from keeping

21   people alive, the only other thing that you want to do

22   is influence the quality of their life, and

1   specifically when you're talking about therapy for

2   diseases, you're looking to change something about the

3   disease that is adversely affecting the quality of

4   that life.

5   And I want to distinguish between the

6   overall concept and direction of assessing the quality

7   of the patient's life, distinguish that from health

8   related quality of life questionnaires, which are

9   specific instruments, but that I would suggest that

10   everything that you talked about, in fact, are

11   snippets or pieces of things that adversely influence

12   quality of life.

13   Now, I think the reason this is important

14   is that, you know, so, for example, if you're talking

15   about symptom scores, well, I think you said that

16   symptoms are only important if they're important to

17   the patient, and it really is implicit in there if

18   it's altering, affecting the patient's life.

19   So edema, for example, might or might not

20   be an important symptom if it's not adversely

21   affecting life.

22   Now, those symptom scores are incorporated

1 into quality of life questionnaires, although

2 generally they try to take it a step further and

3 assess the degree to which the symptom is influencing

4 the patient's life.

5   So I would like to propose that actually

6 what we've got here is a set of measurements all

7 directed toward assessing whether or not the disease

8 is affecting life adversely and whether or not the

9 therapy is benefitting. We can look at scores related

10 to symptoms that are clinically relevant. We can look

11 at how the patient performs on a treadmill as an

12 indication of whether or not they're conducting their

13 daily living appropriately, if we believe that. We

14 can look at questionnaires under certain

15 circumstances, and we can count the number of times

16 the patient is hospitalized on the grounds that

17 hospitalization adversely affects the patient's life

18 as well.

19   And so all of these are things that are

20 aiming at trying to figure out what's important to the

21 patient.

22   CHAIRPERSON PACKER: Udho.

1   DR. THADANI: I'm surprised that either

2   the investigator or independent assessor should be

3   responsible for quantitating. The patient comes to

4   you because he's short of breath or he's fatigued.

5   These are patient symptoms, and I think they're the

6   ones who should be the assessors how they are feeling.

7   And you know, obviously we sometimes as

8   investigators give them leading questions of how many

9   blocks you walk or whatever. So I think if the

10   patient can read the form, maybe they're not

11   sensitive. Maybe their drug therapy is no good. So

12   if the patient says he's short of breath when he walks

13   a block, it's his statement. So even NYHA takes all

14   of that into account.

15   So I don't know why an independent

16   assessor should be able to influence if one goes by

17   what patient ticks on the piece of paper.

18   Could you clarify that? Because these are

19   all -- forget about the exercise part, but if you give

20   the patient a symptom, he's fatigued, he's short of

21   breath. Edema may be a sign unless it is limiting.

22   His legs are so swollen he can't walk or he's

1 troubled.

2   Why should the investigator assess

3 differently than -- unless you're biasing the patient.

4 I realize that, but if you just give them a simple

5 form and he can't read the form maybe the nurse or

6 somebody could just read it to him and you tick it,

7 why should it be a classification different?

8   DR. MASSIE: Well, let me give a couple of

9 examples. I mean, first of all, I didn't say that you

10 had to do all of them. I was going through the types

11 of things that have been used for endpoints, and there

12 are pluses and there are minuses.

13   But, for instance, we've tried to ask the

14 patient how they feel in the acute setting with acute

15 IV therapy, and it really has to do with more whether

16 we're giving them too much pain by the way we're

17 sticking them, how their catheter is feeling, all

18 types of catheters, whether or not they're getting

19 disoriented with an ICU psychosis, and the physician

20 probably is in the better situation to assess in that

21 setting whether the patient is better or not because

22 he's bringing not only his assessment of dyspnea, but

1   also his knowledge of the creatinine and a number of

2   other parameters.

3   In a chronic setting, it may be more

4   reasonable to make your primary endpoint a patient

5   oriented one. On an acute setting it may not be.

6   But that being said, where we've used

7   global scores, there seems to be marked concordance in

8   the ACE inhibitor experience and the beta blockers

9   between the physician global score and the patient

10   global score, which could mean that they're not

11   independent measures, that the physician is telling

12   the patient what to say or the physician is listening

13   to what the patient says, hopefully the latter, but I

14   think they're both good measures.

15   And the real question is when you write

16   your protocol, and I don't know how to get into this,

17   but this is, I think, the key part of this question --

18   DR. THADANI: Especially if you're going

19   to --

20   DR. MASSIE -- is you have five or six

21   different measures, three quality of life scales, two

22   symptom scales, New York Heart Association, and you

know, you're right. The committee in the end is going to look through the whole thing and try to sort it out, but they're going to look at what you said is the important one.

And I'm not sure that in all settings the important one is the same one.

DR. THADANI: I agree with you in the acute situation when the patient is acutely dyspneic. In the chronic one I'd give you an example of two days ago.

I was seeing a patient, and he said, "Well, I really can't do very much." According to that maybe, you know, he can't walk a few blocks. He could be Class 3, but I said, "What did you do today?"

He said he walked from the car parking lot without stopping, but I think I'm creating a bias by putting a leading question. Then the objectivity comes in what he did on that particular day, but knowing what he did in the last few days.

So I personally feel since it's a symptomatic driven therapy, short of hospitalization or mortality or objective exercise testing, we should

1   probably leave it to the patient. I'm not talking

2   about science with objectivity. We have a different

3   issue, but I think these are patient symptoms, and I

4   don't think whether an investigator or a blinded

5   observer should make any difference if one just asks

6   the patient to tick what he feels.

7   CHAIRPERSON PACKER: Yeah, I actually

8   think this is sort of a silly conversation because

9   these two are incredibly interdependent. The way that

10   a patient feels is filtered through how the questions

11   are framed and how the physician asks them, and in the

12   vast majority of cases, there is no direct -- you

13   know, a patient doesn't fill out the case report form.

14   So there's a filtering process here, and

15   that filtering process is inevitable. The reason that

16   they're highly correlated is because there is both an

17   observer based reason why they're highly correlated,

18   and presumably a clinically based reason why they're

19   highly correlated, and I don't think anyone should

20   pretend that these are independent assessments, nor

21   should anyone pretend that any of the assessments that

22   Barry   has   suggested   are   independent   assessments.

1   They're, you know, correlated to varying degrees.

2   I think that the reason why there's so

3   many is because none of them are perfect, and none of

4   them present a complete picture, and in fact, if there

5   were one terrific one, then Barry would have said,

6   "This is really a terrific one," and the guidelines

7   would say there's really a terrific one, and there

8   just isn't one like that.

9   Ileana.

10   DR. PINA: Just to amplify on that, many

11   of these instruments have never been tested in

12   different populations, and so you don't know (a) the

13   reproducibility. You don't know if you can capture

14   even small changes in how the patient feels or how

15   much they're able to do, and that's why you may want

16   to select a few whose specifications do apply to the

17   population that you're studying.

18   Asking somebody how do they feel about not

19   being able to work when they're really a Class 4

20   patient, they may not have worked for years. It may

21   not be as relevant as to someone who was recently

22   diagnosed and can't work.

1   CHAIRPERSON PACKER: Let me just ask

2   everyone a question which everyone is talking around

3   but has not directly addressed.

4   I think everyone in this committee thinks

5   that because there are five or six possible ways of

6   assessing clinical status and they're all, in part,

7   correlated and certainly interdependent. How do you

8   design a statistical plan to deal with that?

9   Because Ileana made a very important

10   point.   She says, you know, we feel very, very

11   comfortable if all of these measures were to be

12   concordant, and I heard you specifically say that, and

13   also heard you specifically not define what concordant

14   meant.

15   I   mean   it   could   be   directionally

16   concordant.   It could all have a certain P value or

17   whatever, but I think the idea is that you had to get

18   the sense that everything was internally consistent.

19   The problem is that you could then take

20   five measures -- I'll just use the word "five"

21   arbitrarily -- and say that there are five primary

22   endpoints or you could pick one that you think sort of

1   has the greatest likelihood of success and say that's

2   the primary and four are secondary, or you can take

3   your alpha and split it, or you can do a whole host of

4   things.

5   And that may sound like an artificial

6   question because Ileana would say, "Well, maybe it

7   doesn't matter what you specify as the primary.

8   You're going to look at the internal consistency and

9   concordance regardless.

10   But there is the issue of alpha spending

11   here, and what you say is the most important, and part

12   of the reason that the composite is mentioned here is

13   the composite is an approach, not the approach to

14   trying to get a mixture of measures, but making it one

15   measure so that the alpha is preserved.

16   Can Lloyd and Tom and Dave help us here?

17   Because we think that these are all reasonable

18   measures, all of which have limitations and

19   inadequacies. We would feel better if they were

20   internally concordant. We would have perhaps some

21   difficulty picking one above all the others. You

22   didn't say that, but I think that you feel that way.

1   You know, what is the solution? What are

2   the options available to the sponsors in the design of

3   clinical trials?

4   Lloyd.

5   DR. FISHER: Well, number one, there are

6   a number of existing options. There are standard

7   things for multivariant endpoints like weighting them

8   equally, combining them all. You could take the

9   minimum P value, for example, adjust for all of the

10 multiple comparisons. You could take the average.

11   But the best way to do this, but the

12 problem is it would just take a phenomenal amount of

13 time, in my opinion. I've thought quite a bit about

14 this strength of evidence. It would be sort of to

15 take every possible pattern of outcome, including the

16 variability in the test, not just the estimated

17 effect, and present it to this panel and say, "Here's

18 two outcomes. Which of these two is more convincing

19 evidence of treatment effect?"

20   And get a one dimensional ordering, which

21 would be very, very complex because it would integrate

22 all of the medical knowledge. If you had that one

1 dimensional ordering, then we would attach

2 probabilities to the top five percent using something

3 called the randomization test.

4 The problem is getting anyone to put in

5 the time and effort to do this. It might be possible,

6 however, to begin to approach this to get some idea of

7 the tradeoffs.

8 We've seen in recent history that

9 consistency isn't necessarily enough. If you miss

10 your primary endpoint, that gets into the middle of a

11 huge debate.

12 And so, I mean, something has to be done.

13 It's best if it's done prospectively, and the best

14 solutions, I think, have not yet been developed

15 because it's somewhat subject matter specific, and it

16 doesn't just involve the statisticians. You have to

17 get people very knowledgeable clinically in the field

18 to help you set up what things are more impressive

19 than others.

20 As Tom said, and he's absolutely right, it

21 doesn't make sense that if you have a placebo in one

22 dose and you have .02, you say, "Ah, ha, we've shown

1   it." You have two doses. They're each significant at

2   the same .02 level. This is more evidence in favor of

3   the drug, but if we do the usual statistical

4   adjustment, you know, we say, "Gee" -- well, I guess

5   not .02 because Bonferroni would do it -- .03, and

6   you'd say, "Gee, too bad. You just missed it."

7   CHAIRPERSON PACKER: Lloyd, I was hoping

8   to hear something other than we haven't solved this

9   problem yet.

10   (Laughter.)

11   DR. MASSIE: Let me just try something

12   out. Let's say we have five scores.

13   DR. FISHER: But let me say one thing.

14   There are ways to solve the problem, and the best ways

15   involve ordering. If you think mathematically and

16   apply the outcomes, you think you're in this five

17   dimensional space.

18   You want to decide what sorts of outcomes

19   are more convincing than others, and if you do things

20   very simplistically, which is concentrate on one

21   endpoint or average them all, et cetera, that does not

22   really encompass what happens some somebody who knows

1   the field or knows what they're talking about looks at

2   the data because you might look at it and say four out

3   of the five are significant, and this fifth one has

4   this incredible variability that's really not a very

5   good quality of life measurement in this population at

6   all.   We   never   should   have   used   it,   but   as   I

7   mentioned, you have to consider not only treatment

8   effect   of   variability,   but   I   think   there   are

9   solutions, but they would take a lot of time.

10   DR.   MASSIE: Let   me   propose   a   simple

11   solution, but I don't know if it has any validity.

12   This may be a total joke, which is let's say you get

13   three   scores   or   five   scores,   New   York   Heart,

14   composite, you know, the global score of the patient,

15   the global score of the physician, put in quality of

16   life, put in some actual measure of dyspnea on various

17   activities.

18   Everybody gets five and all of whom are

19   either better, worse, or the same at the end of the

20   trial,   and   you   can   then   say,   well,   you   have,   in

21   Treatment A, you have, you know, 37 percent of your

22   people had five better, and you could get something

1   like that.

2   Everybody is classified as to whether or

3   how many they had better, and you get a P value for

4   which group comes out better with your five scores,

5   and you know, how many had five better, four better,

6   three better, two better, one better, or worse, or you

7   could put it all together and you get one composite

8   clinical score.

9   Therefore, you have one primary endpoint,

10   one alpha spent P equals .05. Is that something that

11   one could do?

12   This is not taking into account that we

13   know what's better because I think we don't really

14   know what's better.

15   DR. KONSTAM: You know, without knowing

16   exactly how to do it, I'd just like to second the

17   concept because basically what we're saying is that

18   we're not looking at five different things. We're

19   really looking at one thing, and we're looking at it

20   from five different spots, from five different angles.

21   So, you know, I think however this is

22   approached, I think that it's worth -- and of course,

1   doing it prospectively, identifying, you know, how are

2   we going to -- what kind of hierarchy or what kind of

3   mathematical structure are we going to place on these

4   different parameters of really the same thing that

5   we're trying to look at.

6   CHAIRPERSON PACKER: Marv, as you know,

7   and Barry knows this as well, there have been various

8   attempts to create these composites over the past

9   several years, and each attempt differs, not

10 surprisingly, from every other attempt.

11   One proposal that Barry just said was,

12 well, let's give everyone a five and, you know,

13 measure everything and "compositize" it that way.

14   There have been attempts in the past to

15 combine two or three or four. I think what we're all

16 saying is that there isn't a single perfect measure.

17 If you want to use composites because that is a more

18 comprehensive, maybe less biased way of looking at it,

19 that's okay, but you must specify ahead of time what

20 is in that composite and how it will be analyzed.

21   I think everyone is saying that.

22   DR. KONSTAM: Yeah, Milton.   I agree

1   completely, and let me just add that, you know, every

2   new study that's done, I mean, I guess the

3   investigators or sponsor takes a little bit different

4   approach, and I would contend that it's based on

5   whatever advice they have had or it may be based on

6   the last positive study that's been published or been

7   in their experience.

8   You know, I'd like to suggest that we

9   actually have a couple of therapies now in heart

10   failure that pretty much the entire community is

11   getting to believe work, like ACE inhibitors and beta

12   blockers, and we have an awful lot of studies that

13   have been done with an awful lot of things measured,

14   you know, with those two classes of agents, and I'll

15   go so far as to say that.

16   And it may be worth, you know, now taking

17   a step back and looking at the body of data that we

18   have on these agents and see if we can go and glean

19   how to approach the challenge that Barry is raising.

20   CHAIRPERSON PACKER: And, Marv, you may or

21   may not know, but actually Bob Temple asked me to do

22   that, I guess, a year ago.

1   DR. KONSTAM: I should have guessed.

2   CHAIRPERSON PACKER: And without getting

3 into any details about what was a very detailed and

4 long analysis that went on for pages and pages, the

5 short of it is if you look at all of the trials of

6 what might be deemed effective drugs, and by the way,

7 in the analysis what was deemed an effective drug was

8 a drug that ended up being approved by the FDA for

9 heart failure, totally arbitrary definition.

10   (Laughter.)

11   CHAIRPERSON PACKER: But, you know,

12 there's probably a correlation between the FDA

13 approval and efficacy; that if one did that, the two

14 measures that emerged as being the most sensitive to

15 a treatment effect was New York Heart class and the

16 global assessment across the board.

17   Exercise tolerance was very --

18   DR. CALIFF: Where can we find this in the

19 literature?

20   DR. LIPICKY: Milton, you didn't do --

21   CHAIRPERSON PACKER: You can't find this

22 in the literature.

1   DR. LIPICKY: Milton, you didn't really do

2   what's being talked about.

3   CHAIRPERSON PACKER: That's right.   I

4   approximated it.

5   DR. LIPICKY: What you did was look at

6   each thing individually.

7   CHAIRPERSON PACKER: That's right.

8   DR. LIPICKY: And you decided whether it

9   was positive or negative on some basis.

10   CHAIRPERSON PACKER: That's right.

11   DR. LIPICKY: And then you had yes/noes,

12   and what you're talking about is having some kind of

13   a graded thing that puts it all together.

14   DR. MASSIE: Yeah, but this would be the

15   preliminary data that decided how you would design the

16   things you had put in the composite score.

17   CHAIRPERSON PACKER: The difficulty in

18   doing the analysis the way that you might want it done

19   or Marv would ideally want it done is that not all

20   measures were evaluated in all trials, and that's a

21   huge problem.

22   Quality of life instruments were not part

1   of every trial. How do you -- what do you do with

2   that missing data? You can't deal with that.

3   DR. LIPICKY: Right.

4   CHAIRPERSON PACKER: You can't deal with

5   that statistically.

6   DR. LIPICKY: But as I heard the question

7   that you formulated about half an hour ago, it was if,

8   in fact, all of these things measure a patient's

9   interaction with their environment, how could they all

10   do what they did here if, in fact, nothing happened at

11   all or it went in the adverse direction, and that is

12   really looking at all of the data concomitantly, not

13   at any one of them separately, and then drawing

14   conclusions for any one separately.

15   CHAIRPERSON PACKER: That's right.

16   DR. LIPICKY: So there has been no look --

17   CHAIRPERSON PACKER: That's right.

18   DR. LIPICKY: -- at the past data from the

19   vantage point of would it work if you tried to do

20   that. I don't know.

21   CHAIRPERSON PACKER: Right. No, that's

22   correct because what was not available to me at the

1   time this was done was the individual data basis.

2   What was available to me were the summaries submitted

3   by the sponsors on behalf of the drugs, and of course,

4   the analyses submitted by the sponsors were taken at

5   face value.

6   DR. LIPICKY: Correct.

7   CHAIRPERSON PACKER: So but at least it's

8   -- I don't want to even remotely consider it to say

9   that it's an adequate representation of what Marv and

10   Barry are suggesting, but it was the first step in

11   that process in terms of a literature review has been

12   taken.

13   DR. KONSTAM: Just out of curiosity, did

14   you look at drugs that don't work as well as drugs

15   that do work?

16   CHAIRPERSON PACKER: The problem with

17   doing drugs that don't work, there's a real problem.

18   One, there aren't too many NDAs submitted

19   for drugs that don't work.

20   DR. COHN: Well, how are you defining --

21   DR. LIPICKY: Don't work and work.

22   DR. COHN: No, I think this is serious.

1   CHAIRPERSON PACKER: Jay, let's just --

2   the idea was to work with the database, and the only

3   database I could get was a database that was FOI-able.

4   DR. LIPICKY: And those are approvals.

5   CHAIRPERSON PACKER: Right, and those are

6   approvals. So there was an operational limitation of

7   what one could get their hands on.

8   DR. KONSTAM: Well, remembering what you

9   said, the New York Heart Association and global --

10   CHAIRPERSON PACKER: Yeah.

11   DR. KONSTAM: -- assessment, I would

12   suggest that I'm not sure what we learned from that

13   because I think all you're saying is that in the

14   groups of agents that have been approved, those things

15   got better.

16   CHAIRPERSON PACKER: The only reason why

17   that statement has some significance other than being

18   circular, although it may appear to be circular, is

19   that in none of the trials that were submitted as part

20   of the NDAs for approval was New York Heart class or

21   the global assessment the primary endpoint.

22   So what was interesting about the process

1   of review was that the primary endpoint in almost all

2   of the trials was exercise tolerance, which may or may

3   not have been favorably affected by therapy.

4   New York Heart class and the global

5   assessment was almost invariably measured as a

6   secondary endpoint. So, in other words, it could have

7   been entirely self-fulfilling in that the primary

8   endpoint, if it was favorably affected, led to an NDA,

9   but that's not the case here.

10   DR. LIPICKY: But if you say that you're

11   going to try to look at them all together, the

12   designation of primary and secondary is irrelevant,

13   and indeed, the way you started to look at it, there

14   is no method that has been applied to that data. So

15   one doesn't know how it would come out.

16   CHAIRPERSON PACKER: And in order to truly

17   be able to do this right, one shouldn't limit their

18   database, their analysis to a trial submitted as part

19   of NDAs.

20   DR. LIPICKY: That's correct.

21   CHAIRPERSON PACKER: One should ask every

22   sponsor who has done a trial in heart failure, whether

1   or not the trial worked or not, to submit the database

2   so we could use as comprehensive a database as

3   possible.

4   DR. LIPICKY: So how can we work out a

5   method? Does anyone have a suggestion?

6   DR. THADANI: Milton, what about the

7   trials in which the drug had adverse effect on

8   mortality and might have improved your NYHA? Have you

9   included those or just --

10   CHAIRPERSON PACKER: Oh, yeah, all the

11 trials that led -- this --

12   DR. THADANI: But you said only approved

13 drugs.

14   CHAIRPERSON PACKER: Yeah.

15   DR. THADANI: And these are drugs which

16 have not been approved.

17   CHAIRPERSON PACKER: No, no, no.

18 Flosequinine was in the database. There were five

19 trials with flosequinine and drug was approved.

20   DR. THADANI: So what you're trying to

21 say, that there's a dichotomy even with your symptoms

22 called to the outcome. I mean you know.

1   CHAIRPERSON PACKER: Udho, it's a totally

2 separate question.

3   DR. THADANI: But no, no. You're saying

4 that exercise doesn't go along, and that's why

5 exercise is a bad parameter, because it doesn't jibe

6 with symptoms core necessarily, and yet symptoms core

7 doesn't gibe with mortality.

8   CHAIRPERSON PACKER: No, Udho. You're

9 confusing two separate issues.

10   DR. THADANI: Okay.

11   CHAIRPERSON PACKER: I simply described

12 what was done, which was entirely limited and

13 circumscribed based on what was available to be

14 analyzed.

15   DR. LIPICKY: So who will provide the

16 requisite statistical input? I'll volunteer to try to

17 get the data. Who will do it?

18   PARTICIPANT: Do what?

19   DR. LIPICKY: Give the statistical input.

20 There's a statistical method that has to be evolved.

21 You have to somehow another test the null hypothesis

22 looking at all of the data simultaneously. ETT is

1 part of that.

2 DR. FISHER: Well, Ray, if I could get the

3 databases and you would support the program or no

4 support for me, I would analyze the data.

5 DR. LIPICKY: Well, I will support the

6 program morally and intellectually. Do you mean

7 financially?

8 (Laughter.)

9 CHAIRPERSON PACKER: Let me just say that

10 there's another issue here, which makes the analysis

11 even more complex. If one looks at the literature and

12 looks at all of the trial submitted as part of

13 approved NDAs, the analysis of New York Heart class or

14 global assessment or exercise tolerance in trials done

15 in the 1980s is not necessarily the way that data

16 would be analyzed in 1990.

17 DR. LIPICKY: No, that is absolutely true,

18 but that has nothing to do with trying to work out a

19 method and seeing if the data that exists, in fact,

20 would say that these drugs work because right now the

21 data that exist do not say these drugs really work

22 outstandingly, right? I mean, it's a very tough call.

1   So the question is if you took that same

2 data, looked at it with a different method that was

3 everything together, would that change your impression

4 of what the power of those data are?

5   Then you could argue about whether it

6 would be reasonable to apply that method to current

7 data because the medical milieu changed, but at the

8 present time, we're not accomplishing anything.

9   CHAIRPERSON PACKER: Jay?

10   DR. COHN: Can I make a couple of comments

11 here? Because this is a very difficult area, and each

12 of these measures that have been surfaced, exercise,

13 quality of life, symptom scores, et cetera, do not

14 vary in concert, as we well know.

15   However, if one looks at the subgroup that

16 has a marked improvement in quality of life or an

17 exercise tolerance, one finds that all of the measures

18 then do vary together so that the magnitude of effect

19 is very important in convincing us that this is a real

20 change.

21   And one of the problems that we've had in

22 looking at prior trials is that we have focused on P

1   values of the significance, say, of the improvement of

2   exercise, even though the magnitude of that effect is

3   minuscule, but the P value comes out less than .05,

4   and we, therefore, conclude that the drug is

5   effective, and that's within the noise range, and it

6   is not reproducible, and it's luck of the draw often

7   more than anything else.

8   And, in fact, when one looks at mean

9   responses of all of these variables in the trials that

10 we have carried out to date, the magnitude of effect

11 is very small, and yet the magnitude of effect on

12 mortality and morbidity has turned out to be very

13 large.

14   So that symptoms and quality of life are

15 very poor markers for effective therapy in this

16 disease. Now, what I would suggest is an alternate

17 way to analyze it, and that is to really focus on

18 since not all patients respond the same to a drug --

19 I mean, this is a broken record, and we all know that,

20 but we pay lip service to it.   We don't often

21 incorporate it into our thinking process -- it would

22 be perhaps more useful to look at those individuals,

set above which you're going to look at the endpoint and say let's find out between the placebo and the treatment arm how many people improve above this threshold level where we're confident that is a real effect.

And that gives us a lot more comfort in knowing what fraction of patients are going to get better rather than trying to look at a mean response in the large population where the changes are very small and there's a lot of noise.

And when you do that, I think you'll find that most of these measures will vary in concert.

CHAIRPERSON PACKER: Bob.

DR. TEMPLE: Well, it's certainly worth trying that, but my prediction is it won't help you at all. If you set response characteristics and say, "Okay. This much is a good response. This much is a weak response," you'll find the same thing.

The problem here is that there's tremendous variability in both the treatment and placebo groups. That's why the means aren't very different. You'll also find the categorical responses

1   won't be very different either.

2   That's a prediction. We haven't done it

3   that way, but that's what you're going to find.

4   DR. COHN: But you would get the number of

5   responders rather than the mean response.

6   DR. TEMPLE: You will, but it'll be closer

7   than you want even though you think these drugs work

8   because the mean responses and the categorical

9   responses are closely related.   If one were very

10   different, then the other would be very different,

11   too.

12   I just want to make one point.   Nobody

13   should be too surprised at this. You find the same

14   thing in almost every therapeutic area we look at.

15   It's characteristic in trials of antidepressants to

16   look at four separate measures of depression. There's

17   a global, and there's a specific depression scale

18   measure, and there's a section of the depression scale

19   and so on, and you see the same kinds of things.

20   There's tremendous variability from study

21   to study and imperfect consistency within a study.

22   You see the same thing with antihistamines in allergic

1   rhinitis.

2   These diseases are hard to categorize, and

3   there's a lot of day-to-day variability. It may not

4   be that it's because the drugs don't work very well or

5   the measures are poor. It just may be characteristic

6   of the way life is.

7   The other thing, Milton, is what I

8   remember is your analyses of the ACE inhibitor trials,

9   and I thought all of the endpoints were about equally

10   good or equally poor depending on how you look at it,

11   not very much difference between them in how likely

12   they were to be positive. New York Heart wasn't all

13   that much different from exercise.

14   CHAIRPERSON PACKER: Yeah, Bob. I guess

15   what I should have said before I even said that there

16   was any tendency for one measure or another is that in

17   no case was a single measure consistently indicative

18   of a drug effect in all trials done with that agent.

19   DR. TEMPLE: Right, but the other thing to

20   remember is your test was was this result significant,

21   and you didn't try to get into did it lean right and

22   other questions that one could get into.

1   CHAIRPERSON PACKER: And frequently it

2   leaned right, but didn't have a nominal P value

3   associated with it.

4   All of these can only be addressed by what

5   Ray was saying before, which is get the data and

6   actually do the analyses.

7   I will honestly tell you that such a

8   project is an immense undertaking.

9   DR. TEMPLE: Could we make very clear what

10   the project is to do? I'm a little vague on that.

11   DR. LIPICKY: I see it perfectly. It's

12   two phases. One phase is for somebody who knows

13   statistics, math, and probability to sit down and

14   decide how the null hypothesis would be denied when

15   you look at all of the things together and say how

16   could it be that these numbers went in the direction

17   they went if, in fact, this treatment did not alter

18   the state of the patient. I mean that's really the

19   question.

20   The second part of the project is to by

21   patient by patient get the primary evaluations of each

22   thing that was evaluated, every patient's symptom

1   score, every patient's New York Heart class for every

2   visit so that you can start with raw data because

3   there's no way to reconstruct change from baseline,

4   which probably is the analysis that would need to be

5   done on an individual-by-individual basis on the means

6   that are usually submitted in data.

7   So you'd have to get all of the trials'

8   raw data together and try this method on it and see if

9   -- because certainly the way Milton approached it made

10   it look dismal, right? I mean we all agree with that.

11   DR. TEMPLE: No, I don't think it looked

12   dismal.

13   DR. LIPICKY: Well --

14   DR. TEMPLE: It looked like what I

15   predicted it to look like.

16   DR. LIPICKY: Well, fine, but that is

17   dismal.

18   DR. TEMPLE: But that is depression.

19   DR. LIPICKY: Right.

20   DR. TEMPLE: It looks like depression. It

21   looks like antihistamines. It looks like angina. It

22   looks like everything.

1   DR. LIPICKY: Look. Depression is not the

2   sine qua non of knowledge, right?

3   DR.   TEMPLE: It   looks   like   every

4   symptomatic measurement I know of.

5   DR. LIPICKY: Fine. That's fine, but that

6   may be because no one looks at the data they collect

7   properly, and if it were looked at properly for drugs

8   that really work, it would be obvious. The thing

9   that's being said is the way in which we usually treat

10   this data may not be the way it should be treated, and

11   is there another method that could be devised to look

12   at it differently?

13   DR. TEMPLE: I mean, that's possible, Ray,

14   but there's one crucial thing to remember on this, is

15   these are all measurements of exactly the same thing,

16   and that makes --

17   DR. LIPICKY: Well, I understand that.

18   DR.   TEMPLE: These   are   not   remotely

19   independent measurements. What you've got is the same

20   thing with a lot of noise. That makes a very tough

21   thing to analyze, I think.

22   DR. LIPICKY: Well, and you may be right.

1   That is, if someone went to the effort of doing what

2   is being talked about, it would turn out to lead to

3   nowhere. I mean I don't know that it would do --

4   DR. FISHER: Well, one comment on Jay's

5   approach. It can certainly be done, but it will

6   increase sample size substantially to define the

7   people you're sure are responding and compare those

8   proportions.

9   DR. THADANI: Ray, surely this is a

10   biological variation. We wake up in the morning. We

11   can't sleep at night. We feel lousy. The next day we

12   don't.

13   So you know, all of these will have a lot

14   of noise just because of the biological variation.

15   It's not necessarily the method is not good. The

16   question is how you, as you said, statistically put

17   this biological variation to be confident over a

18   period of a one-year trial and what you're doing is

19   really true or not.

20   CHAIRPERSON PACKER: That's why we have

21   placebo groups.

22   DR. THADANI: But that's why I'm saying.

You do a placebo. If you don't beat it, it's just the

drug is no better, but again, the problem even with a

placebo, you're assessing the patient every three

months on that day when he comes to the clinic, and I

assure you a lot of people don't even remember what

they did four days ago, leave aside how they were

feeling a month ago.

So I think those are the reasons why none

of these measures are good enough.

CHAIRPERSON PACKER: We need to bring this

to a closure, but I want to end on, I guess, hopefully

three brief discussion points.

The first one, just, Jay, you made the

statement that the effect on morbidity and mortality

with drugs for heart failure tends to be large. The

effect on symptoms tends to be small.

All of us who use drugs for heart failure

have the impression that these drugs have a greater

symptomatic benefit than is revealed by the trials.

In other words, for example, we get the impression

that ACE inhibitors make people feel better more than

the trials that show a change in New York Heart class

1 or global assessment or exercise tolerance to an ACE

2 inhibitor.

3   So I hold out the hope that, in fact, the

4 drugs are making people feel better, but our

5 instruments are so insensitive to picking out effect,

6 which is why the delta between the two groups on any

7 individual measure is small.

8   DR. COHN: I think diuretics make people

9 feel much better, and the adding things to diuretics

10 have a very small additional effect.

11   CHAIRPERSON PACKER: I'm glad you

12 mentioned diuretics because that's discussion point

13 number two.

14   DR. TEMPLE: Milton, before you leave that

15 one, how can you believe that what you detect

16 clinically is more reliable than what you detect in a

17 controlled trial?

18   CHAIRPERSON PACKER: Oh, I didn't say it

19 was more reliable.

20   DR. TEMPLE: Well, why do you believe that

21 these drugs make people feel much better than turns

22 out to be the difference between the drug and the

1   placebo group in the trial?

2   CHAIRPERSON PACKER: I was engaging in

3   wishful thinking.

4   DR. TEMPLE: Ah.

5   (Laughter.)

6   DR. TEMPLE: Okay.

7   CHAIRPERSON PACKER: That's all right.

8   DR. KONSTAM: Can I comment also, Milton,

9   because there's something I've been wanting to say?

10   I think that I'd like to see an urging --

11   PARTICIPANT: Into the mic.

12   DR. KONSTAM: I thought I was. Oh.

13   I'd like to see an urging of a movement

14 away from physician determined assessments of symptoms

15 and quality of life, such as the New York Heart

16 Association class and the global assessment. It

17 actually sort of concerns me that those were the two

18 that popped out of your analysis.

19   And I think that actually your comments

20 about, you know, what we see as clinicians, I think,

21 speaks to this, which is that, you know, these

22 assessments bring in substantially the bias of the

1   physician incorporating all sorts of things that may

2   have no importance to the patient at all.

3   And just to throw it out, I think that

4   this was a concern in the beta blocker data set and

5   the carvatelol data set because if you know that the

6   patient's heart rate is lower, I think you may

7   subconsciously or not be more likely to, say, give a

8   higher score for the global assessment.

9   So I see, you know, in the document, you

10   know, at least as I read it, there is no preference

11   really given to which of these different scales, and

12   I would like to urge a preference for patient

13   determined scales as opposed to physician determined

14   scales.

15   CHAIRPERSON PACKER: Marv, I'm glad you

16   picked up on the fact that there was no preference

17   because, in fact, great pains were taken to make sure

18   that the positives and negatives, the limitations of

19   each of these, were simply described without a

20   hierarchy being created because one felt that it would

21   be hard to do that in any kind of evidence based

22   manner.

1   And remember the global assessment is

2   particular complex because it can be done by the

3   patient or by the physician, but that even if the

4   patient does it, it's still translated through an

5   observer.

6   There is a patient global assessment.

7   DR. KONSTAM: That's not always -- well,

8   I'm not sure what you mean by that. I mean if, for

9   example, you give a quality of life questionnaire --

10   I'm not trying to support any particular quality of

11   life questionnaire, but there you're asking the

12   patient to fill it out or you're transcribing the

13   patient's responses.

14   I think that's different from asking the

15   physician to check off, you know, where do you think

16   the patient sits in terms of your global assessment

17   and New York Heart Association class.

18   CHAIRPERSON PACKER: No, and Barry did, by

19   the way, have the global assessment on both the

20   investigator and the patient end --

21   DR. THADANI: Milton, this might be

22   relevant. The patient comes to you for a symptom. We

should just stick to the patient improvement.

A patient could come to me. He said, "I'm feeling lousy." I listen to his chest. His chest is clear. He looks fine to me.

I say, "Oh, you're doing great," and then your assessment is completely ruined. So I think there's a lot of biases in that.

We should rather than making composite, we should keep it very simple. You do a trial because patient is short of breath. He's got fatigue or he can't do X amount of things. Keep those as one, two, three. Give it a score, whatever you want, and that's your primary -- if you want to make it a primary endpoint, make that.

And if you can't beat the placebo, so be it. I mean, that's life. The patient has come to see you for those specific things.

CHAIRPERSON PACKER: The purpose of this guideline is not to tell people what their primary measure of efficacy should be. The purpose of this document is to describe what efficacy measures have been used and have been used with varying degrees of

1   success, and in the absence of a universal view as to

2   which should be preferred, and I haven't heard a

3   universal view as to which would be preferred, the

4   document speaks for itself, and the --

5   DR. THADANI: Maybe they're wrong.

6   CHAIRPERSON PACKER: And the sponsor --

7   and the sponsor can put forward anyone that they wish

8   to evaluate. They're going to evaluate others as

9   well, and we're all going to be able to look at the

10   consistency of data just as Ileana emphasized earlier.

11   DR. KONSTAM: Well, Milt, maybe we should

12   have a little bit of discussion about this point

13   because I personally would like to see a hierarchy.

14   I'm arguing that I think that physician determined

15   assessments of symptomatology are suspect relative to

16   patient driven measures, and maybe we should have a

17   little bit of discussion about whether we'd want to

18   incorporate some kind of hierarchy into that.

19   CHAIRPERSON PACKER: Is exercise tolerance

20   a patient or investigator determined assessment?

21   DR. KONSTAM: I mean, it's an objective

22   measure. It's not --

CHAIRPERSON PACKER: It's neither -- to tell you the truth, it's neither patient -- it's neither entirely patient or investigator.

DR. KONSTAM: Yeah, I should have been more clear. I guess I'm referring to measures of -- I think exercise test I see as a separate measure that has an objective quality to it.

I'm referring more to measures of -- other types of symptoms, such as the global assessment scores or judgment of the New York Heart Association class, which are much less objective, which are really very subjective on the part of the physician. Those are the ones that I'm concerned about.

CHAIRPERSON PACKER: Marv, you know, if I -- and I'd love to get a sense from the group -- but in all honesty, without having have everyone sort of take a look at what the data are, I'm not certain that the document can actually express a preference at the present time.

Let me just say I think that everyone in the audience has heard your sense that you think that the patient determined measures would give you a

1   higher degree of confidence, but if someone wanted to

2   use an investigator determined measure as the primary

3   and still measure the patient and they were

4   consistent, you would still feel very comfortable.

5   DR. KONSTAM: No, I'm saying that I might

6   not feel comfortable at all; that if that were the

7   only measure that was an indication of a symptom

8   effect, I would be, in fact, very uncomfortable that

9   the physician is simply incorporating something into

10   the assessment that may not be important at all.

11   And so I guess, you know, I --

12   CHAIRPERSON PACKER: Well, why don't we --

13   I think maybe the best way of addressing that, and I'm

14   trying to do this hopefully in a way that solves

15   problems without creating more, is for the document to

16   emphasize that both patient and physician based

17   assessments should be performed to look at the

18   consistency of the effect across both of those.

19   DR. THADANI: I think physician does

20   signs. He can't assess. The patient feels how he

21   feels. The physician is only assessing signs. He

22   can't change how the patient is feeling. I mean, he

might change his opinion, but I think that's the wrong

way to do it.

I think physicians to stick to whether the

lungs are clear, you know, how much the patient weighs

when he comes to the clinic, but I don't think he

should be assigning in my judgment you look great so

you're feeling better.

I think the patient assessment -- we

should stay away from this assessment by the physician

of the patient.

DR. MASSIE: The physician's assessment is

not meant to be the physician's assessment of how the

patient feels. It's his assessment with his best

knowledge of all the measurements of how the patient

is.

DR. THADANI: But to give you a lot of

biases --

DR. MASSIE: Well, I agree. You have

biases.

DR. THADANI: But I think there are too

many biases.

DR. MASSIE: But I can tell you patients

1   get biases, too, and they may have to deal with the

2   meal that was served. I don't think you can look at

3   one only. That's why I was trying to get a handle

4   on --

5   DR. THADANI: Why not? Why not? I mean

6   a patient comes to you for one symptom. Why can't you

7   look at that?

8   DR. MASSIE: Because he can't remember

9   what it was like two weeks ago.

10   CHAIRPERSON PACKER: No, no, this is going

11   nowhere.

12   (Laughter.)

13   CHAIRPERSON PACKER: Unless someone tells

14   -- unless I hear a consensus in this committee for a

15   stated   preference   for   investigator   determined

16   measures, then the document has no choice but to

17   remain neutral and not speak to this issue, and I have

18   heard both Marv and Udho say that they would like the

19   document to specifically state a preference for a

20   patient derived measure.

21   Does anyone agree?

22   (Show of hands.)

1   CHAIRPERSON PACKER: Okay. There are

2   three amongst -- how many would feel comfortable

3   having the document stay neutral?

4   (Show of hands.)

5   CHAIRPERSON PACKER: Okay. I think we'll

6   just keep it neutral, and anyone who listens to this

7   discussion can reach their own conclusions.

8   Dan.

9   DR. RODEN: I have a couple of points that

10   I wanted to make that are probably redundant, but I

11   felt like I had to say something.

12   (Laughter.)

13   DR. RODEN: Firstly, the idea of a

14   composite score, well, to be serious for a second, the

15   idea of a composite score has some appeal because of

16   this issue of spending alpha if you looked two or

17   three times, but it seems to me that until the heart

18   failure community comes to grips with the fact that

19   they don't understand the pathophysiology of the

20   disease they are studying completely, then the scores

21   have to reflect that uncertainty.

22   And so it may be that when you combined

three or four different scores, you might be combining

two or three of them that are measuring, in fact, the

same thing and one that's not. So you end up with a

composite score which, while appearing to be

clinically useful, may actually not be as useful as

you think.

And that sort of leads me back to two

other comments. One is that everything we know about

the scores and how they turn out is based on past

history, and when new therapeutic compounds come

along, it may be that they will perform well with

different scores that haven't yet been developed. I

think that's written into the document though.

CHAIRPERSON PACKER: Yes.

DR. RODEN: And then, I guess, the last

comment I have to make is to sort of echo but in a

different way what Bob Temple said, and that is this

issue of day-to-day variability in the disease and its

response to therapy.

You know, I think that reflects both the

fact that we're treating this thing called heart

failure, which I think is many diseases, and if you

1   could figure out how to subset them, and when somebody

2   like Jay or Milton or someone figures out how to

3   subset them, then it may be that you'll be able to

4   develop very, very directed therapies that take all of

5   that variability away.

6   So it's another plea for rather than

7   lumping all of this clinical entity together in one

8   big pot, but to continue to have an open mind to

9   underlying mechanisms.

10   CHAIRPERSON PACKER: Bob and then Lloyd.

11   DR. TEMPLE: I guess I just want to remind

12   everybody that even what we're talking about now

13   represents a radical departure from previous history.

14   Up until now, the usual primary endpoint

15   in these trials was exercise testing, and the reasons

16   for that were it was thought to be at least somewhat

17   less susceptible to influence of unblinding and things

18   like that, and I'm not sure it's necessarily time to

19   abandon that view.

20   It's not that there weren't sometimes

21   exceptions to that in certainly outcomes. Outcome

22   effects were always considered an additional and

wonderful endpoint if you could get them.

But all of the drugs that were approved, basically just ACE inhibitors, were approved primarily based on their exercise test finding. Now, it's true not every study showed it, but many did, and the ones that didn't were sort of leaning, and that was not considered a tragedy.

And so I want to remind everybody that it's not quite clear to me why we're abandoning the thought that that's not a particularly good endpoint since it sort of is measuring an important thing.

DR. LIPICKY: But what's being talked about is not abandoning that.

DR. TEMPLE: I'm sorry. I didn't hear you.

DR. LIPICKY: What is being talked about is not abandoning that.

DR. TEMPLE: Well, it's reducing its primacy a little bit.

DR. LIPICKY: Well, no.

DR. TEMPLE: No?

DR. LIPICKY: Anyone can still choose to

1   make ETT their primary endpoint. No one said they

2   couldn't.

3   DR. TEMPLE: But the urging --

4   DR. LIPICKY: What has been discussed is

5   what if somebody chose the doctor's global evaluation

6   as their primary endpoint.

7   DR. TEMPLE: What I'm saying is --

8   DR. LIPICKY: Or is there some other way

9   of making symptoms more analyzable.

10   DR. TEMPLE: There is more than one way to

11   express that view. One is to say ordinarily you

12   should plan on studying exercise testing, but if you

13   want to make the case for some other endpoints, do it,

14   or you can say it's a free for all. Do whatever you

15   want.

16   I'm just pointing out that this is a

17   change and just reminding people of that.

18   The other thing that Barry dropped in --

19   DR. LIPICKY: But it isn't a change

20   because that's what people were always told, Bob.

21   Whenever people came in for a heart failure trial --

22   DR. TEMPLE: Why did they always pick

1   exercise?

2   DR. LIPICKY: Whenever people came in to

3   talk about a heart failure trial, they were told, I

4   think, in so many words, nobody knows what to measure.

5   You need to choose a primary endpoint because the

6   statisticians don't know how to handle things when you

7   have more than one.

8   (Laughter.)

9   DR. LIPICKY: And --

10   PARTICIPANT: We know how to handle them,

11   but you aren't going to like it.

12   DR. LIPICKY: And ETT -- and ETT is not a

13   bad thing because it's the primary complaint, and

14   obviously you need to evaluate it. It would be crazy

15   to not.

16   So you can choose that, but if you want to

17   choose something else you can.

18   DR. TEMPLE: Right, but if you go back and

19   look at previous guidance that we've written in draft

20   form on heart failure, it emphasizes exercise

21   tolerance more than these other things. I'm just

22   pointing out that this represents a change.

1   And the other thing I want to mention is

2   what Barry dropped in without any subsequent

3   discussion, the idea that symptomatic improvement

4   needs to be shown in studies of six to 12 months. The

5   number of studies that have ever done that is, to my

6   best knowledge, zero, except when the exercise or

7   other symptomatic improvements were part of an outcome

8   study.

9   So that's something that needs some

10   discussion. That's a very challenging symptom study.

11   CHAIRPERSON PACKER: Let me --

12   DR. TEMPLE: And one needs to ask if it

13   really can be done.

14   CHAIRPERSON PACKER: Yeah, Bob, let me

15   clarify two things because I think Barry was

16   summarizing the document, and the document actually

17   says things in a certain specific way. So let me see

18   if I can do this.

19   First of all, with respect to the history

20   of exercise tolerance and without getting into an

21   extensive review of all of the public and non-public

22   discussions that may have ever taken place on this

1   topic, I think it would be fair to say that the

2   previous guideline dated 1987 for heart failure, which

3   is the only prior written document on this, had a

4   heavy emphasis on exercise tolerance.

5   DR. TEMPLE: That's right.

6   CHAIRPERSON PACKER: Which does not exist

7   in this document.

8   DR. TEMPLE: That's what I was remarking

9   on.

10   CHAIRPERSON PACKER: Period. It does not

11   exist in this document, and that non-hierarchical

12   approach to exercise tolerance is intention, and it is

13   a reflection of how people feel about how to evaluate

14   drugs   for   heart   failure   and   their   general

15   disappointment   with   the   utility   of   --   general

16   disappointment with exercise tolerance as being any

17   better than any other measure of efficacy.

18   But Ray is right. There is nothing in

19   this document that says you shouldn't measure exercise

20   tolerance   or   you   couldn't   put   it   as   a   primary

21   endpoint, and you certainly could. So this document

22   is flat, non-hierarchical on which of these measures

1   and perhaps all of these measures combined or assessed

2   collectively could be taken.

3   All this document says is there really are

4   more than one ways to do it. They're all imperfect.

5   All you have to do is pick one or more, and whatever

6   you do, say it up front so that an appropriate

7   analytical plan can be devised.

8   And I guess -- and I don't want to really

9   get into this -- but this document does not say that

10   all of these measures need to be made. So, for

11   example, I imagine that if a sponsor came in with some

12   symptom assessment, and let's not specify what that

13   is, analyzed in an appropriate prespecified fashion,

14   which was considered by this committee to be

15   persuasive, and never measured the effect of the drug

16   on exercise ever, that would be okay.

17   Right, Ray?

18   DR. LIPICKY: Reluctantly, yeah.

19   (Laughter.)

20   DR. TEMPLE: Well, I'm not sure I agree

21   with that.

22   CHAIRPERSON PACKER: Really?

1   DR. THADANI: Milton, you are knocking

2   exercise because the mortality went in the wrong

3   direction because until --

4   CHAIRPERSON PACKER: No, no, no. I guess

5   I'm -- I just want to make sure that I understand.

6   Since guidelines in general have offered people a

7   sense of what works and what doesn't work, I guess,

8   Bob, I would ask you: if someone believed that they

9   could show a treatment effect based on New York Heart

10   class, global assessment, quality of life, whatever

11   symptom evaluation they want, and they just said,

12   "Listen. We really have very little faith in exercise

13   tolerance. We don't want to do it. We'll give you

14   two, three, four trials which use this symptom

15   assessment. The draws are internally consistent and

16   persuasive," why would anyone ever have to measure

17   exercise tolerance?

18   DR. TEMPLE: Well, I'm not prepared to

19   argue that that's impossible, but if you remember our

20   carvatelol discussions, there was great skepticism

21   about the globals because of concern that they were

22   more unblindable and influenceable than other things,

1   and I don't think that concern should -- that concern

2   hasn't gone away from my point of view.

3   A very well documented symptom focused

4   quality of life scale might be very good. I might be

5   more comfortable with that, but I don't think it's a

6   grab bag in which everything is equal.

7   The other thing, I just wanted to follow

8   up on what Dan was suggesting before. When you take

9   all of these symptoms and try to make a composite out

10   of them, what you're actually doing is, I think,

11   taking a sort of integrated look at things that are

12   themselves variables. So you reduce the variability.

13   But when we think of a composite score

14   like we take death plus MI plus stroke, you're really

15   adding up separate things. That is not what this

16   would be.

17   This would be an attempt to say these

18   individual scales are all sort of crummy. I'm going

19   to look at them all together. By taking all five and

20   averaging them, it's sort of integrating and dividing

21   or something like that, which may not be a bad idea,

22   but I guess I think we still need some more work on

1   which of these scales are more susceptible to

2   influence and other questions.

3   I'm not sure there is no hierarchy yet.

4   I don't know.

5   DR. LIPICKY: Just a minute to defend ETT.

6   I mean, you know, the best way I can think of of

7   making people not have symptoms is to put them to bed

8   and keep them asleep. Now, that is not a treatment

9   for heart failure.

10   DR. RODEN: It actually is.

11   DR. LIPICKY: Well --

12   (Laughter.)

13   DR. LIPICKY: Fine, I understand.

14   CHAIRPERSON PACKER: It used to be.

15   DR. LIPICKY: I understand, but if it is

16   drug induced, that drug isn't to treat heart failure.

17   So the ETT, in fact, assures that the heart is tested

18   during exercise and that the drug which is being used

19   to treat the heart failure is not decreasing the

20   activity level, which would clearly make people feel

21   better without actually affecting any aspect of the

22   pathophysiology or the heart.

1   So I think there is room for ETT. It is

2   desirable, but if you pin me and say, you know, "Gee,

3   somebody comes in and proves that everybody feels

4   terrific. You have enough assurance that this didn't

5   put them to sleep," you know, I think ETT is symptom

6   relief, and it is nothing more than symptom relief,

7   and you'd have to consider that.

8   CHAIRPERSON PACKER: I don't think we're

9   going to -- I mean, clearly all of these decisions

10   will be very data dependent based on what the NDA is,

11   but your conclusion, I think, Bob, is an accurate one,

12   which is the previous preference for exercise is gone

13   in this guideline, and I get the sense that people are

14   comfortable with that.

15   That is not to abandon exercise, but it's

16   to say that we don't feel that the previous preference

17   was justified.

18   DR. TEMPLE: Just to follow up on what Ray

19   said though, there are components of how you feel that

20   relate to whether you can do more, and there are other

21   components that might be differently described. It

22   does seem to me that it's relevant to ask people or

measure it by exercise whether you can, in fact, do

more.

Now, some of these measures like globals

may have that as a component and some might not, and

if they didn't, I think that's a problem.

CHAIRPERSON PACKER: As you know, New York

Heart class is inherently that kind of question.

DR. TEMPLE: That's not bad, right, and

the gradations are pretty --

DR. LIPICKY: But it is -- just one word

more. You know, it is important to measure. I mean,

beta blockers are beta blockers with alpha adrenergic

properties also, clearly decrease exercise tolerance,

but they make people feel better, and that's okay. It

doesn't have to increase exercise tolerance, but I

think it should be evaluated.

CHAIRPERSON PACKER: Ileana, yes, please.

DR. PINA: I mean, I have to sit here and

defend ETT as well. You know, exactly what Dan said,

some of the measures that we've used in the past may

not be applicable to today, and just like we don't

have an ideal quality of life measurement, we don't

1   necessarily have an idea exercise test, and all of the

2   early exercise tests were based back on the old

3   anginal trials where you walked five minutes. Well,

4   now did you walk six, six and a half?

5   That maybe didn't make any sense, and this

6   is where the six minute walk came from and the nine

7   minute walk.

8   So I would use exercise tolerance as

9   another part of this feeling better, able to do more

10 score, but I also don't want people to leave here

11 thinking that it's not important. I think it is

12 important.

13   DR. THADANI: But it's an objective score,

14 isn't it? I think the way this document is written,

15 exercise is being knocked, you know, completely

16 negative.

17   You know, if you read the second

18 paragraph, it says it is really no good. I think

19 exercise is an objective way of measuring it. I know

20 there are patients walk better. They walk longer than

21 placebo. Great. I think they should be able to do

22 more.

1   So I don't think we should completely --

2   the way it is written probably has to be changed, that

3   paragraph. That's a useful measure, and it should be

4   in addition to your symptom score.

5   CHAIRPERSON PACKER: Udho, I disagree with

6   what you've said. The limitations of every single one

7   of these assessments is emphasized.

8   DR. LIPICKY: Right.

9   CHAIRPERSON PACKER: Exercise is not --

10   the global assessment is described in terms of its

11   limitations. Quality of life is described in terms of

12   its limitations, and everyone should know what the

13   limitations are.

14   And I don't think that it would be useful

15   to have this discussion go any further because I think

16   the document speaks for itself.

17   Let me just emphasize the issue of

18   diuretics.   There's something that needs to be

19   clarified. Does this document apply to diuretics,

20   Ray?

21   DR. LIPICKY: I think it does.

22   (Laughter.)

1   DR. LIPICKY: Well, you asked me to not be

2   negative.

3   CHAIRPERSON PACKER: Okay.

4   DR. TEMPLE: Milton.

5   DR. LIPICKY: Diuretics are for the

6   treatment of heart failure, right?

7   DR. TEMPLE: There is some ambiguity here.

8   CHAIRPERSON PACKER: Yes, I know.

9   DR. TEMPLE: The most recent diuretics

10   that have come through have been labeled for fluid

11   accumulation associated with boom, boom, boom. So

12   what we looked at is weight loss --

13   DR. LIPICKY: So this is the most radical

14   change.

15   DR. LIPICKY: -- in people with heart

16   failure. They weren't really claiming symptomatic

17   improvement.

18   CHAIRPERSON PACKER: Speaking now from the

19   perspective of how many applications for diuretics

20   this committee has seen --

21   DR. LIPICKY: One.

22   CHAIRPERSON PACKER: -- which is one --

1   DR. LIPICKY: But let me just amplify my

2   statement. I see no reason that this should not be

3   applicable to diuretics. Okay?

4   Now, if someone developed a diuretic and

5   brought a new drug application to the agency and said,

6   "All I know is it makes people pee," I think we would

7   need to consider that also, but there is no reason

8   that any of the things that are said in this document

9   or any of the measurements that are suggested that can

10 be made in this document are not equally applicable to

11 diuretics as they are to something that affects the

12 heart or the vessels.

13   CHAIRPERSON PACKER: Maybe I should -- we

14 need some clarification on this because up to now

15 diuretics have been based on their ability to increase

16 urine or they have been approved based on their

17 ability to increase urine output and decrease weight

18 or decrease edema.

19   DR. LIPICKY: Correct.

20   CHAIRPERSON PACKER: All of which are

21 either physiologic endpoints or physical signs.

22   DR. LIPICKY: Correct.

1   CHAIRPERSON PACKER: And there has been no

2 database that I know of as part of an NDA that has

3 been directed towards symptoms --

4   DR. LIPICKY: Correct.

5   CHAIRPERSON PACKER: -- or outcomes.

6   DR. LIPICKY: But if someone brought a

7 diuretic in that showed that people felt better or

8 could exercise longer or had a longer duration of life

9 or had fewer hospitalizations, we would not approve it

10 because it doesn't fit the guideline?

11   CHAIRPERSON PACKER: No. No, it would fit

12 the guideline then.

13   DR. LIPICKY: Yes. So I'm saying this is

14 applicable to diuretics.

15   CHAIRPERSON PACKER: That would mean those

16 were the first diuretic ever approved for the

17 treatment of heart failure.

18   DR. LIPICKY: I understand that. You

19 asked me the question is this applicable to diuretics.

20   CHAIRPERSON PACKER: Oh, okay.

21   DR. LIPICKY: The answer is yes.

22   CHAIRPERSON PACKER: Let me try one more

1 time.

2   DR. THADANI: How would you do that?

3 Because it's background therapy?

4   CHAIRPERSON PACKER: Is there another way

5 other than this guideline by which diuretics can be

6 approved?

7   DR. LIPICKY: Yes.

8   (Laughter.)

9   CHAIRPERSON PACKER: Okay. Do you want to

10 clarify that any further?

11   DR. LIPICKY: Yes. They just have to show

12 that they are a diuretic, and that salt and water

13 comes out of the body and body weight goes down and

14 that it is able to be kept stably down, and that

15 people don't dry up and become a prune.

16   CHAIRPERSON PACKER: Rob? I have a

17 feeling you have something to say about this.

18   DR. CALIFF: Well, I mean, once you have

19 a diuretic which has been shown to save lives in

20 patients with heart failure, is it a safety problem or

21 an efficacy problem if another diuretic just makes

22 people pee in a situation that made the things

1   differently to surrogate endpoints like electrolytes

2   or neurohormonal status?

3   CHAIRPERSON PACKER: What state are we in

4   now?

5   DR. LIPICKY: That's a really good

6   question.

7   CHAIRPERSON PACKER: Do you think there's

8   been a diuretic that's been shown to do those things?

9   DR. LIPICKY: No, no, no.   What he's

10 saying is --

11   DR. CALIFF: Well, yes.

12   DR. LIPICKY: -- if a diuretic that worked

13 up according to these guidelines and showed that it

14 saved lives in congestive heart failure and another

15 diuretic after that came along and showed that you

16 made more urine and that's all they showed, would the

17 rules change?

18   CHAIRPERSON PACKER: I think the situation

19 would be more interesting if someone developed a

20 diuretic which made people pee and didn't make people

21 feel better or increased mortality.

22   DR. CALIFF: But if all you've got to do

1   is show that you made people pee, that takes ten

2   patients.

3   DR. MASSIE: Yeah, but we're not going to

4   get a placebo control trial long term of a diuretic.

5   DR. CALIFF: We have one.

6   DR. MASSIE: Even though no one has shown

7   that.

8   DR. CALIFF: I thought we had one --

9   DR. LIPICKY: Well, look. I mean --

10   DR. CALIFF: -- that's just been stopped

11   for benefit.

12   DR. MASSIE: Well, that's not a pure

13   diuretic.

14   DR. CALIFF: Oh, it's not a pure diuretic.

15   DR. MASSIE: Or else it would have been a

16   long term trial.

17   DR. CALIFF: What diuretic is a pure

18   diuretic? Don't pills that we give people affect

19   everything downstream from the blood that it's in?

20   DR. LIPICKY: Well, I don't know if you

21   want to really take this away from the current

22   document. You're raising real problems that would

1   take long times to talk about.

2   CHAIRPERSON PACKER: I think what we hear

3   you say, Ray, is, just to try to keep this focused,

4   that the concept of a diuretic could be approved based

5   on changes in physiology or physical findings remains

6   in place.

7   DR. LIPICKY: No, no. It isn't physiology

8   or physical findings. I mean to show people who are

9   edematous lose 15 pounds is as good as people being

10   able to run longer around a treadmill, right? I mean

11   that's a real thing.   It isn't physiology or

12   pathophysiology. It is the management of edema, and

13   that's as good a measure of whether it does that as it

14   is to say symptoms are better if you can run 30

15   seconds longer on a Bruce.

16   So I don't think it's appropriate to

17   characterize it as a physiological thing or a

18   surrogate thing. It is the management of edema, and

19   there's no better way to know whether you're managing

20   it than if body weight doesn't change.

21   It doesn't say at the present time it has

22   not been necessary in the past to document long term

1 symptom benefit or morbidity or mortality, and that is

2 an applicable statement to the last diuretic that was

3 approved, which I believe was 12 years ago.

4 CHAIRPERSON PACKER: Torsemide was four

5 years ago.

6 DR. LIPICKY: Four years ago? Okay. It

7 got started six, okay, quite some time ago, about the

8 time or just a little after the time that the major

9 treatment for heart failure was approved on the basis

10 of a single exercise tolerance trial.

11 DR. THADANI: Ray, surely --

12 DR. LIPICKY: Okay? So you don't want to

13 start making too much of a contrast here, and

14 certainly this guideline would be applicable to a

15 diuretic. One could develop a diuretic for the

16 treatment of heart failure following the instructions

17 for use here. There is another way in which they can

18 do it.

19 DR. THADANI: One of the difficulties I'm

20 having is if you look at all of the symptomatic heart

21 failure ACE inhibitor trials, a diuretic has been

22 background therapy in all of them. So I even don't

know if ACE would work without a diuretic in symptomatic heart failure --

DR. LIPICKY: That's correct.

DR. THADANI: -- if you go by objective data.

So you are stuck with doing diuretic active control trials. You can't do placebo controlled trials. You use diuretics in patients not only for --

CHAIRPERSON PACKER: That's not the issue we're discussing.

DR. THADANI: No, no, but you can use diuretics for patients who are short of breath, have few pulmonary rills, don't have edema. So you don't have to lose four pounds in order to approve it. There are different indications.

DR. LIPICKY: Well, you can do that, Udho, but we haven't approved a diuretic --

DR. THADANI: I realize that, but diuretics are part of the background therapy. How do you get around that for approval process?

You are suggesting there should be active

1   control trials against a fixed regimen.

2   DR. LIPICKY: No, I haven't suggested

3   anything.   This guideline says you can do placebo

4   controlled trials, you know.

5   DR. TEMPLE: Udho is getting to the

6   question of how you'd actually bring it off if you

7   wanted to since you can't leave the diuretic out

8   easily.

9   DR. LIPICKY: No, I understand.

10   DR. TEMPLE: And an active controlled

11   trial would be uninformative.

12   DR. LIPICKY: That is merely a topic, you

13   know, for another day.

14   CHAIRPERSON PACKER: Okay. Look. We have

15   one remaining issue on symptoms which Bob brought up

16   and Barry addressed. The time frame of the clinical

17   status trials is stated in the document to be six to

18   12 months as opposed to what used to be three months.

19   That, if it stands, would represent a

20   conceptual change, and we should discuss that briefly.

21   DR. TEMPLE: Right.   It's worth

22   remembering that all of the approved products were

1   based on data not more than three months, except

2   insofar as symptomatic data were collected as part of

3   an outcome study. Then you got longer data, but they

4   were all three month data.

5   CHAIRPERSON PACKER: Carvatelol was six

6   months.

7   DR. TEMPLE: Well, Carvatelol was a little

8   exception. The exercise tolerance didn't work out

9   there. Some of those data are longer.

10   DR. MASSIE: But I think it's not so

11   contradictory. I mean among the more radical changes

12   are the degree of information we want to know about

13   morbidity and mortality either as efficacy or as

14   safety, but one way or another we do need to know

15   that.

16   And I think it's impossible to get that

17   data in three month trials. We now realize that that

18   type of information evolves over time, and so I think

19   it's not -- I mean, I don't think you'd want to have

20   two pivotal trials looking at symptoms in three

21   months, and then how are you going to get your 4,000

22   patients of exposure over long term? So I think it

1   makes sense to --

2   CHAIRPERSON PACKER: We shouldn't --

3   DR. TEMPLE: Those are different studies.

4   CHAIRPERSON PACKER: We shouldn't confuse

5   efficacy and safety.

6   DR. MASSIE: Right. Well, but what I'm

7   saying is that it doesn't make sense not to collect

8   longer term data if what you want to know at the end

9   of the package is something about longer term

10   experience.

11   DR. KONSTAM: No, but, Barry, if exercise

12   time happens to be the indicator that supports the

13   symptom improvement, you're not going to necessary --

14   and that were acceptable at three months -- you could

15   acquire the survival data over much longer without

16   getting more exercise tests after six months.

17   DR. MASSIE: Well, you could, and I think

18   the other reason why Milton probably expanded this to

19   six months is we've watched beneficial effects

20   dissipate between three and six months, and

21   flosequinine is probably one for sure, although we

22   didn't quite measure it at six months again.

1   And the question is: why three months?

2   Why not six months?

3   I mean, it was three months because -- I

4   mean, the way this all works is one study came out

5   well, got a good response from the FDA, worked well

6   for patients, and for the next ten years people copied

7   that protocol.

8   And   then   you   get   the   beta   blocker

9   protocols where the same things that worked well for

10 the ACE inhibitor ten years ago don't work well, and

11 all of a sudden we have a new paradigm.

12   Maybe there's nothing magic about either

13 paradigms, but we have learned that exercise tolerance

14 effects tend to disappear over time with some drugs.

15   PARTICIPANT: Well, they are two different

16 issues. That's the problem.

17   DR.   TEMPLE: Well,   no,   but   that's

18 misleading. That was a drug that was progressively

19 killing people.   Maybe that's why the exercise

20 tolerance went down.

21   I mean that's not quite the ‘ame thing,

22 and I just want to --

1   DR. MASSIE: It's not quite the same

2 thing, but the question is: do you care if exercise

3 improves in three months and it isn't improved in six

4 months?

5   DR. KONSTAM: Well, whatever time frame is

6 arbitrary. You could say the same thing about one

7 years, Barry.

8   DR. TEMPLE: Another way of describing

9 what you're interested in is to make sure it improves

10 exercise over a reasonable period of time and then

11 gain assurance from larger, longer studies on outcome,

12 which is historically how it's been done.

13   CHAIRPERSON PACKER: Maybe the document

14 should say that periods of time should be three to 12

15 because the issue about assessing what the mortality

16 is going to be assessed now regardless. Whether it's

17 neutral, positive, negative, it doesn't matter. It's

18 going to be assessed long term in a controlled

19 fashion.

20   So do you feel comfortable with three to

21 12?

22   PARTICIPANTS: Yes.

1   DR. TEMPLE: Yeah, well, given that choice

2   most people will go with three, you know.

3   CHAIRPERSON   PACKER: Well,   not

4   necessarily. Some drugs may not have much of an

5   effect in three. The effect may get greater over

6   time.

7   DR. TEMPLE: Sure. That's always --

8   CHAIRPERSON PACKER: Yeah.

9   DR. TEMPLE: Can I ask one other question

10   about the survival question? Does that apply equally

11   to all classes of drugs?

12   CHAIRPERSON PACKER: Different topic.

13   DR. TEMPLE: Okay.

14   DR. FISHER: Milt, can I --

15   CHAIRPERSON PACKER: Yes.

16   DR. FISHER: -- as a question? When I was

17   looking at the endpoints that you have, there was only

18   one thing I expected to see that I didn't, and that

19   was in the worsening heart failure. What about a

20   patient that slowly declines and ends up getting

21   tremendous increases in the concurrent meds., but

22   who's not hospitalized? Is there any level at which

1   that would be considered worsening heart failure?

2   CHAIRPERSON PACKER: The difficulty, and,

3   by the way, that is the next topic, so let's hold that

4   for a second, and we're going to ask Jay to review the

5   Section 5.2, which is evaluation of long term outcome.

6   And, Jay, although this wasn't

7   prespecified, what I'd like you to do is review this

8   not only from an efficacy point of view, but from a

9   safety point of view. I'm sure you just -- do

10   efficacy first, and then move on to, after we're done

11   with that discussion -- because we are not going to

12   formally discuss the safety part of this document, but

13   the long term effects of drug are a safety issue even

14   if one is only looking for a symptomatic indication in

15   the intermediate term.

16   So we'll split the discussion into two

17   parts. The first part, just focus on efficacy, and

18   then we'll pause and then go on to long term outcomes

19   as a safety issue.

20   DR. COHN: Well, I'm not sure you can

21   separate them that easily because efficacy and safety

22   are obviously related.

1   CHAIRPERSON PACKER: That's fine.

2   DR. COHN: Let me put in perspective what

3   I'm going to say because, first of all, we all have to

4   sit here agreeing that heart failure is a biological

5   process, and we've spent a good deal of time talking

6   about symptoms and quality of life and exercise, which

7   bear a very poor relationship to the severity of the

8   biological process, first of all. We all recognize

9   that.

10   You   can   have   an   advanced   biological

11   process with very few symptoms. You can have a very

12   modestly advanced biological process with a lot of

13   symptoms.

14   And when we talk about the first few

15   months after therapy has been initiated and we're

16   looking for symptoms relief or some measure of

17   efficacy, we're really looking for evidence that our

18   drug has altered the relationship between the

19   biological process and the symptoms because in a very

20   short period of time, in a few months, the biological

21   process may not progress very much, and you're now

22   trying to change the relationship between the

1   biological process and the symptom complex.

2   If you look later on, nine and 12 months

3   out, when there is clear evidence that the biological

4   process has progressed -- and I'm going to show you

5   some slides if anybody -- is there somebody up there

6   to show slides? -- then you may be looking at the

7   favorable effect on the biological process which would

8   lead to symptom relief.

9   So a three month symptom benefit and a 12

10 month symptom benefit may be mechanistically entirely

11 different, and I don't think we should mix them

12 together.

13   DR. LIPICKY: There is someone up there

14 now.

15   DR. COHN: Okay. So my theme is really

16 going to be that we're dealing with a lot of disparate

17 endpoints, and it is not, I don't believe, appropriate

18 to say, "This drug works. Therefore, let's find out

19 how everything fell together," because drugs don't

20 necessarily work on all aspects of this disease, both

21 short term and long term.

22   Now, the biological process is still an

1   enigma, and we know that, and I'm going to suggest in

2   the second paragraph of 5.2 that the statement, the

3   last sentence of that second paragraph has to be

4   watered down, and instead of saying that -- the term

5   "surrogate" was used -- that surrogate endpoints have

6   not yet been shown to reliably predict the effect of

7   drug because they haven't, but we should not close the

8   door to this in the future, and that, therefore, they

9   cannot currently be used in lieu of direct measures of

10   clinical benefit.

11   I think that's only fair because I'm

12   hoping that in the work-up of drugs in the future that

13   we're going to see a lot of these physiologic markers

14   measured so eventually we will be able to link them to

15   clinical outcomes and thus simplify and shorten the

16   process of demonstration of drug efficacy.

17   The first slide, if somebody is up there

18   to show a slide, I mean, this is just my initial

19   candidates for the biological process, and at the

20   moment there are probably three general candidates

21   that we use to assess the severity of the disease.

22   One   is   the   structure   of   the   left

1   ventricle, which relates to its function, of course,

2   and that's ejection fraction of N diastolic and N

3   systolic volume or mass or perhaps even histology.

4   The level of neurohormonal activation, and

5   that means norepinephrine and perhaps naturetic

6   peptide levels, endothelan, many others that are

7   candidates for that, maybe gene expression.

8   And something in the electrical area which

9   we know plays a role in sudden death, VTAC,

10   repolarization dispersion, depolarization dispersion,

11   some aspects of VP, and we've got experts on the

12   panel.

13   Next slide.

14   Now, this is what I mean about the

15   biological process. This process progresses like

16   this, and you enter a study somewhere along the way of

17   that biological process, and if it progresses and

18   leads to a heart failure death, you die, but along the

19   way you may die prematurely from an electrical or some

20   other mechanism, and death, of course, is not a very

21   simple endpoint for the biological process, and it's

22   a surrogate marker for the disease, but the disease is

1   the biological process if we could monitor it.

2   And when you at entry in a very short

3   period of time show that a patient has gotten better,

4   you're modifying the symptoms in relationship to the

5   biological process, but you're not intervening

6   necessarily on the slope.

7   If you have a drug which changes the

8   biological process, you may favorably affect the slope

9   or unfavorably accelerate the slope and cause death

10   prematurely.

11   So it isn't a very simple thing to look at

12   one endpoint, such as death, or symptoms and assume

13   that they are going to go in the same direction. You

14   may have a drug which favorably affects the biological

15   process, but increases the risk of sudden death, and

16   mortality may be a very poor marker for what that drug

17   has done.

18   You may reduce heart failure deaths and

19   increase sudden deaths, and then if you put a

20   defibrillator in all of those patients, you'd now get

21   the benefit of the improved slope of progression

22   without the sudden death, and that's, of course, a

1   future possibility.

2   So we have to open our eyes to all of

3   these co-therapies that may influence the disease.

4   Now, let me just give you an example of

5   one drug in which the combined endpoint would get you

6   into terrible trouble. Can I have the next slide,

7   please?

8   Here is vesnarinone. Now, the vesnarinone

9   trial is a beautiful dose titration trial in which

10   placebo in red, vesnarinone in 30 milligram dose and

11   vesnarinone 60 milligram dose were tested, and there

12   is a dose dependent increase in mortality or reduction

13   of survival, and the P value for the vesnarinone 60

14   versus placebo is highly significant.

15   Now, this essentially scuttles this drug

16   as a useful agent to treat heart failure, and at the

17   end of the trial about five percent more patients

18   randomized to vesnarinone 60 than to placebo died. So

19   over five years or, let's see, over two years average

20   -- this is what? A couple of years -- over those

21   couple of years five more percent of the people died.

22   Now, the next slide.

1   Now, when we looked at the mean changes in

2   quality of life at the first 16 weeks, there was a

3   highly significant benefit of vesnarinone 60. It

4   waned by 26 weeks, but for the first 16 weeks, this

5   group significantly got better compared to the placebo

6   group.

7   Now, if we tease them out -- next slide --

8   and just look at those whose quality of life improved

9   by a dramatic amount, and we arbitrarily chose an

10   increase of 15 or improvement in 15 units in the

11   Minnesota Living with Heart Failure questionnaire

12   because that is a number in which there is absolutely

13   no overlap in reproducibility from test to test, and

14   it is two standard deviations beyond any noise.

15   Now you look at what happened at eight

16   weeks in all the patients on placebo versus all the

17   patients on vesnarinone, and there's about five

18   percent of these people; more of them got better than

19   the placebo group. So it's about the same number who

20   would increase their mortality if they were followed

21   over all the period of time. We have no idea if this

22   is the same group of patients. It may be two entirely

1   separate populations that we could have identified.

2   But if we look just at the Class 4

3   patients who all say that they want improved quality

4   of life and they don't care about mortality -- at

5   least that's been the previous experience with this

6   patient population -- look at this. There's an 18

7   percent difference. That is, on placebo 20 percent of

8   the Class 4 patients got better at eight weeks,

9   whereas 39 percent of the vesnarinone patients got

10   better at eight weeks, suggesting that for some reason

11   this drug produced a dramatic effect in quality of

12   life. That is, it had some benefit on symptoms with

13   the same biological process, but it did not favorably

14   affect the biological process. In fact, the mortality

15   increase was all sudden death. So it didn't change

16   probably the biological process, but it increased the

17   risk of sudden death.

18   Now, the final point, I was going to make

19   this before. When we looked at all cause mortality

20   plus hospitalization, which is put forward in the

21   guidelines as a composite endpoint that's more

22   powerful than mortality alone, the adverse effect of

1   vesnarinone disappeared.

2   Why? Because the drug did not adversely

3   affect the slope of the biological process. It caused

4   sudden death, and therefore, there was no increase in

5   hospitalizations.

6   So when you add hospitalizations to

7   mortality, the difference between placebo and

8   vesnarinone disappeared.

9   So you have to be very careful when you

10   design a trial to choose the endpoint that you think

11   you will win on, and if you had chosen a combined

12   endpoint in this trial, you would have had a neutral

13   effect, whereas, in fact, the drug is having an

14   adverse effect on mortality.

15   So mortality, morbidity, sudden death,

16   quality of life, all may vary disparately, and it's

17   not easy then to assign a single score, a single

18   global marker for efficacy in heart failure. It's

19   very difficult to say, "I have a treatment for heart

20   failure that works."

21   You tell me on what it is working. Is it

22   working on the biological process in slowing it? Is

1   it working on the electrical abnormality and reducing

2   sudden death events? Is it improving quality of life?

3   You tell me what it is doing, and very few drugs do

4   all of these things to a comparable degree.

5   And, therefore, the design of a trial, I

6   think, is going to have to be very much dependent on

7   the proposed mechanism of action of the drug and the

8   proposed endpoint that you feel you are most likely to

9   win on.

10   And my sense is that the agency is

11   perfectly happy to accept whatever endpoint you choose

12   as long as it's in some way related to morbidity or

13   mortality or quality of life, and you've got to be

14   sure you guess right, and no rigid document is going

15   to tell you what to use for any given drug.

16   CHAIRPERSON PACKER: Does that mean you

17   liked or didn't like the document?

18   (Laughter.)

19   DR. COHN: I'm suggesting that the

20   document, that in some aspects it has to be softened,

21   and I think the use of a combined endpoint may in some

22   instances work very well if you're influencing the

1   biological process.

2   If you have a beta blocker and you believe

3   it is altering the biological process of progression,

4   then obviously using a combined endpoint is going to

5   be far more powerful than looking for any single one,

6   but if you have a drug which is working on

7   arrhythmias, you would not choose a combined endpoint

8   because you're probably going to lose.

9   CHAIRPERSON PACKER: As far as I can

10   recall, and perhaps I should make sure, the document

11   does not create a preference for a combined over

12   mortality.   It is so perfectly reasonable to analyze

13   mortality alone or a composite.

14   The document does state that one probably

15   shouldn't analyze hospitalizations alone because it

16   doesn't include the worst event that could occur.

17   That's more of the competing risks issue.

18   DR. COHN: Yeah.

19   CHAIRPERSON PACKER: And certainly your

20   choice of which one you would like needs to be

21   tai'ored to the kind of drug you're using and may also

22   be   tailored   as   to   whether   you're   making   this

1   evaluation in order to demonstrate a treatment effect

2   or to reassure people about the safety of a drug.

3   DR. COHN: Yeah. There's one more point

4   I meant to make, too, and that is in terms of analysis

5   because if one seeks out a single answer to the

6   efficacy of a therapy, it invites you to do what is

7   said in the principles of analysis in 5.3.2, which is

8   that the best way to analyze some nonmortality

9   endpoint is to substitute the lowest possible figure

10   for a patient who died and didn't get the nonmortality

11   measurement made.

12   And that would suggest that we are looking

13   for a global answer to the question of efficacy, and

14   I would suggest that that is an over adjustment which,

15   in fact, in many instances may cloud the issue.

16   The vesnarinone data I showed you asked

17   the question if you survive -- now, let's say five

18   percent more are going to die now -- but if you

19   survive, are you going to be healthier and feel better

20   with the drug than without the drug? Now, that means

21   you've got to weigh. You've got a time adjustment

22   weight that you have to put into all of this in terms

1   of using such a drug, and vesnarinone is a lousy

2   example because the benefit was only 16 weeks.

3   But if you had a drug which produced this

4   sustained benefit in a subset of the patients who took

5   the drug and the cost was that a few more people died,

6   you'd have to weigh these things carefully, and it

7   wouldn't be fair to obliterate the quality of life

8   improvement by substituting for everybody who died a

9   low score because you might then eliminate the benefit

10   on quality of life and not be able to tease out

11   separately the effect of the drug on how people feel

12   in the survivors.

13   CHAIRPERSON PACKER: I know we're going to

14   talk about this, and I know, Tom, you may or may not

15   speak to this issue, but let's hold those comments.

16   This is an analytical analysis issue, Jay. So we're

17   just going to hold that for a moment until we get to

18   that section.

19   Lloyd?

20   DR. FISHER: I wanted to ask you a

21   question about Jay's paradigm because I don't think I

22   buy it, and there are several reasons.

1   One is I think it's extremely difficult to

2 separate the sudden death from the power failure, but

3 I would also suggest it's quit possible that the

4 propensity or probability of sudden death increases

5 with your process.

6   So that it's not like some extra thing

7 that goes along and if you just prevent that, you'll

8 have the gains, whatever. I mean that could be true.

9   Now, I don't follow this literature, and

10 I could readily be wrong, but that's my impression

11 from the little I know, and I'd be interested to hear

12 the other clinicians on the panel.

13   DR. COHN: Well, I didn't mean to suggest

14 that they are separable because, as the disease

15 progresses, the risk of sudden death increases, but

16 there certainly are some drugs that we give and the

17 biological process has not been changed, and shortly

18 after administration of the drug, they get tourisad

19 and die. That's clearly an adverse effect of the drug

20 on the electrical process, not on the biological

21 process.

22   So these two are going on together, and I

1   don't mean to suggest that it is easy to separate the

2   two mechanisms of death.   I just point out the

3   complexity of having a single treatment for the

4   disease process.

5   CHAIRPERSON PACKER: Tom.

6   DR. FLEMING: Jay, your terminology of

7   death and clinical endpoints being a surrogate for the

8   mechanisms of action that you're trying to achieve

9   concerns me in the perspective of what it is that

10   we're about here.   I would state that what we are

11   about is to achieve tangible clinical benefits to

12   patients, presumably and hopefully mediated through

13   intended biological effects on the biological process,

14   i.e., we understand the disease process to an extent,

15   to an extent, to suggest what are at least in part

16   some of the causal mechanisms that lead to the

17   clinical consequences, and we wish to intervene on the

18   patient's behalf to achieve clinical benefit mediated

19   through positive effects on that disease mechanism.

20   So to state that death or clinical

21   endpoints are surrogates for this disease mechanism

22   seems to be reversing the issue here.   The issue is

1 effects on these disease mechanisms or surrogates that

2 you would hope to be able to establish in the future,

3 as you say, for the clinical benefit.

4   DR. COHN: Well, if all deaths were

5 related to the biological process and, therefore,

6 potentially favorably affected by your therapy, you

7 would be right, but of course, when people die of

8 gunshot wounds, they count as deaths on the drug, and

9 we recognize that all deaths are not related to the

10 disease process, are not related to the therapy that

11 you are trying to utilize.

12   So in many ways it is neither a sensitive

13 nor a specific marker for the disease process.

14   DR. FLEMING: But the issue here is that

15 it's not just gunshot wounds. The issue is you can

16 identify and measure certain biological mechanisms,

17 and those mechanisms may, in fact, be causally related

18 to these clinical events that we're trying to affect,

19 but as I've seen in other beautiful transparencies

20 that you've shown, there are a myriad of different

21 mechanisms at play here, some of which may not at all

22 be captured by a given mechanism that you're tracking

1   along your axis.

2   In addition to that, there are a myriad of

3   unintended, unanticipated, undocumented, unrecognized

4   effects of intervention that you are inducing that can

5   also affect the clinical outcome here, all of which

6   are very real and important and not arbitrary,

7   unrelated chance happenings like gunshot wounds.

8   So ultimately if the goal here is to

9   benefit patients in a tangible way, these mechanisms

10   here that you are talking about are surrogates;

11   effects on those are surrogates for the clinical

12   endpoints.

13   A second point, while I have the

14   microphone here quickly --

15   DR. FISHER: Just one thing, Tom. The

16   good news is we've all found a surrogate we'll accept:

17   death. If somebody can show that as a surrogate for

18   helping the disease process, I'm willing to accept

19   that.

20   DR. FLEMING: The second point is the

21   comment that you had made about needing to find the

22   measure that will be most sensitive to the effect of

1   treatment I partially agree with. I think we do need

2   to look for those measures that are sensitive.

3   But we also need to develop what I might

4   refer to as a hierarchy of clinical endpoints:

5   mortality, morbidity, as well as, as we've already had

6   an hour and a half discussion on, a myriad of

7   different measures, symptoms, and quality of life, and

8   those have varying degrees of relevance to patients,

9   and the magnitude and duration of effects that we

10   achieve on those endpoints also influence the clinical

11   importance of effects on patients.

12   And I would argue the goal here is to

13   target those endpoints that are particularly relevant

14   to patients that we would believe will be affected by

15   the intervention.

16   So if, for example, mortality and some

17   measure of symptoms are both affected, to say I'm

18   going to choose the measure of symptoms and ignore

19   mortality is not justifiable based on the hierarchy,

20   mortality being more important.

21   Certainly we want to target measures that

22   we anticipate will be sensitive, and I argue what we

1   should target as our primary endpoint is that measure

2   on the hierarchy of clinical relevance that we expect

3   to be -- the highest that we expect to be particularly

4   sensitive.

5   So, for example, if we think that we are

6   unlikely to positively or negatively affect mortality,

7   I can understand and accept that that's not your

8   primary endpoint. You may choose exercise tolerance

9   or some measure of symptoms, but in a setting where

10   you anticipate mortality to be sensitive or likely to

11   be affected, then I have difficulty ignoring that and

12   targeting a measure such as symptomatic status.

13   DR. COHN: Yeah, I probably trying to be

14   controversial   have   made   overstated.   You've

15   interpreted it as an overstatement.   I would never

16   suggest that we don't monitor morbidity and mortality.

17   However, we are going to be entering an

18   era if, indeed, the current beta blocker trials and

19   perhaps   the   spiranol   lactone   trial   pan   out   as

20   announced,   we   may   find   ourselves   with   an   annual

21   mortality rate in this disease so low that perhaps one

22   point is to say, "Hey, why don't you get it? We don't

1   need anymore drugs," or the other would be to say,

2   "Well, you cannot do 20,000 or 30,000 patient trials

3   carried out over eight years to demonstrate efficacy.

4   We've got to find a simpler, quicker, more sensitive

5   guide to efficacy than waiting for people to die

6   because fewer and fewer apparently are going to die if

7   they're treated with all the therapies that are now

8   out there."

9   So my plea is that we should be looking at

10   the potential in the future of powering a trial for

11   the biological process and looking at these clinical

12   endpoints to make certain that they go in the right

13   direction, but not insisting on the same power, the

14   same P value that we do today because we are not

15   monitoring the biological process.

16   And I would be very comfortable perhaps in

17   the future, not today, and that's why I say we're not

18   there yet, but I would be very comfortable eventually

19   in the future to have a marker for progression of the

20   disease   that   is   clearly   favorably   affected   by

21   intervention, and now the mortality is reduced by 20

22   percent, but I haven't really got enough numbers of

1   deaths to be powered for the P value that we

2   traditionally want that I would say, "Hey, that's good

3   enough now. I'm willing to look at that and accept

4   morbidity and mortality reduction in the absence of P

5   value as adequate once I have the biological process

6   nailed down."

7   DR. FLEMING: I would certainly find it

8   very acceptable to argue that in the setting where you

9   have low risk of mortality and anticipated and

10   ultimately documented effect on symptomatic status or

11   quality of life with supportive evidence that's not

12   significant, but supportive on mortality, that's a

13   strong case. That's a case based on -- not driven by

14   the mechanism issue, but driven by the fact that we

15   have established symptomatic benefit, and we actually

16   over and above that have evidence of positive trends

17   on mortality as well.

18   The surrogate measure that you're

19   assessing certainly gives us plausibility of efficacy,

20   but to do an assessment that is based on a documented

21   effect on a mechanism of action or surrogate endpoint

22   with a trend on mortality is still weaker evidence.

1   DR. COHN: Well, I hope you'll change your

2   mind maybe as data accumulate over the ensuing years,

3   I hope.

4   DR. FLEMING: But I would only change my

5   mind to the extent that the data that accumulates is

6   of a nature that allows us to reliably conclude that

7   documented effects on these biological markers are

8   reliably telling us that we will achieve the intended

9   benefits on the clinical endpoints.

10   DR. COHN: Well, that's why I hope that

11   the guidelines will encourage industry to collect that

12   kind of data that would satisfy you because that's the

13   secret. I mean, we have to collect that kind of data

14   so in the future we're not hung up on the same kind of

15   almost impossible challenge as we are today.

16   CHAIRPERSON PACKER: Jay, obviously I

17   guess my own feeling is that's beyond the scope of the

18   guidelines, but one can take your plea to industry

19   directly now.

20   DR. COHN: Well, the guidelines could

21   encourage collection of that kind of data 'n these

22   trials.

1   CHAIRPERSON PACKER: Well, let me try to

2 refocus what you --

3   DR. COHN: And the agency would look at it

4 as supportive evidence. If there was some statement

5 in the guidelines, then that would be very supportive.

6   CHAIRPERSON PACKER: There are already

7 statements in the guidelines that a whole host of

8 physiologic markers are useful in the characterization

9 of a drug, and certainly if they went in the same

10 direction as the symptom and outcome data, it would

11 not be looked at as being noncontributory.

12   But I think the question -- but you made

13 the statement just a few minutes ago which I think

14 troubles me, and that is that if you had an effect on

15 a marker let's just say we're modeling because it just

16 happens to be the marker of the month that people

17 happen to like, but whether it will withstand the test

18 of time I don't know.

19   If you were markering mortality and found

20 at the end of six months where you had an effect on

21 remodeling, let's say the effect on remodeling is

22 unequivocally present, and you recorded 20 deaths in

1   one group and 20 deaths in another.   Would you

2   consider the mortality data to be confirmatory of the

3   remodeling effect?

4   COHN: Obviously not.

5   CHAIRPERSON PACKER: Twenty and 19?

6   DR. COHN: Well, I mean, you know, you can

7   do this with most anything.

8   CHAIRPERSON PACKER: But you see, that's

9   the problem.   Bob, that's the problem with small

10   numbers.

11   DR. COHN: You'd have to see the whole

12   database, and you'd have to look at a lot of other

13   things besides that, but 20 deaths, of course, is not

14   powered for much of anything.

15   CHAIRPERSON PACKER: Right.

16   DR. COHN: So you obviously might need

17   more, but the question is whether you need Ray's

18   .00125; is that what it is?

19   DR. LIPICKY: Yes.

20   (Laughter.)

21   DR. COHN: Or whether you'd be willing to

22   accept .06 if, indeed, everything else goes in the

1   right direction.

2   CHAIRPERSON PACKER: Oh, I'm sorry. Then

3   okay.   It's not as if an effect on a physiologic

4   marker with a P value of .9 -- that would not be

5   satisfactory.

6   DR. COHN: No, I don't think it would.

7   CHAIRPERSON PACKER: I understand.

8   Lloyd. I'm sorry. Bob.

9   DR. TEMPLE: Well, that last reflects sort

10   of a general principle. Depending on how persuasive

11   they are, other evidence of that kind will be used

12   along with the results of controlled trials to either

13   strengthen or undermine them.   So as a general

14   principle, we're prepared to do that. The question is

15   when it's persuasive, of course.

16   CHAIRPERSON PACKER: Ray?

17   DR. LIPICKY: You know, in the discussion

18   that has occurred in the last five or ten minutes, the

19   topic has changed seven times. I wanted to address

20   the very first thing that Jay said, which I want to

21   sort of support, and that is the natur. of all of

22   these interventions ought to be towards altering the

1   natural history of the disease if one is intending the

2   therapy that way, but it is also to, if one cannot

3   affect the natural history of the disease, to make

4   people feel better. Okay?

5   So there are two components to all of

6   this, and one of the things that is missing in the

7   guidelines and in discussions is how what seems to

8   have public health benefit, such as reduction in

9   hospitalizations or mortality, is, in fact, a measure

10   of affecting either of those things, and how does one

11   know that affecting death is a measure of affecting

12   the natural history of the disease?

13   I'm not sure I know, and in that sense, in

14   that sense, although it may have clinical importance,

15   okay, I think I agree with Jay. It is a surrogate of

16   what we should be interested in.

17   That doesn't mean it is a nonmeaningful

18   clinical measure, nor that it could not satisfy the

19   pragmatic aspects of being a primary endpoint in a

20   trial, but it doesn't mean -- I don't think that

21   anyone can say that one knows that if that variable is

22   affected, one has changed the natural history of the

1 disease.

2   And as a biologist, I think that that's

3 what everybody's interest should be in.

4   CHAIRPERSON PACKER: But not necessarily

5 as a clinician.

6   DR. LIPICKY: Well, if clinicians are not

7 biologists.

8   CHAIRPERSON PACKER: Right. I think

9 the --

10   DR. COHN: They used to be.

11   DR. LIPICKY: They used to be. I mean

12 back in my day.

13   CHAIRPERSON PACKER: I think that the

14 distinction -- I don't want to try and over simplify

15 it -- but the distinction between the position that

16 Jay is describing and the position that Tom is

17 describing is a difference between an emphasis on

18 understanding the disease process from the point of

19 view of a biologist to treating patients who are at

20 risk, which is the point of view of a clinician.

21   Right now the approval process, the

22 evaluation process is taken from the point of view of

1   the clinician. That isn't necessarily -- that is not

2   the only view, and it certainly is not necessarily a

3   view that leads to rational drug development, but it

4   is a view which is very patient oriented, but it is

5   not oriented towards disease understanding.

6   DR. LIPICKY: Right. I think that that's

7   a correct statement.

8   CHAIRPERSON PACKER: Right.

9   DR. LIPICKY: And I must say I agree with

10   Jay in that I object to that.

11   CHAIRPERSON PACKER: Right.

12   DR. LIPICKY: I think that it is bad for

13   us to undermine that interest.   I don't see an

14   alternative unfortunately.

15   CHAIRPERSON PACKER: But I think that's

16   the point. We all would like to be biologists, but we

17   all end up being clinicians.

18   DR. FLEMING: By the way, I'm completely

19   endorsing that the insight of the biologist is key

20   here and that it should be used in guiding drug

21   development, but what I'm arguing is ultimately what

22   should lead to approval of and use of an intervention,

1   the fact that it is biologically active or the fact

2   that it is clinically effective?

3   DR. LIPICKY: Right.

4   DR. FLEMING: The biologist can take the

5   agent that's biologically active, but doesn't provide

6   clinical benefit. I will be happy to take the agent

7   that's clinically effective.

8   Ultimately I try to put myself in the

9   position of a patient when I decide what it is that we

10   ultimately need to show in a clinical trial, and I'm

11   not arguing against the importance of the biological

12   mechanisms as providing us important insight into the

13   interventions that we should be studying and the

14   plausibility of their efficacy, but ultimately I want

15   to document that efficacy before I as a patient am

16   convinced about efficacy and safety.

17   DR. LIPICKY: No, I understand the

18   pragmatic thing, but I think one has to recognize the

19   kind of truth to the statement that although mortality

20   is very attractive, it may be a surrogate for what we

21   really want to know.

22   CHAIRPERSON PACKER: But we are all saying

1   the same thing, reiterating. I'm almost tempted to

2   imagine that someone is going to create a cartoon with

3   a tombstone, the epitaph on the tombstone saying, "My

4   heart was smaller."

5   DR. FISHER: Milt, before we move on to

6   analysis, and I know we all want to preserve a lot of

7   time for analysis, two questions about your endpoints.

8   One was the one I mentioned before, the

9   concomitant meds., if that really changes.

10   And   the   second   thing   is   under

11   cardiovascular events, in such an event as life

12   threatening arrhythmia, a drug would be approved if

13   you reduced life threatening arrhythmia.

14   CHAIRPERSON PACKER: It doesn't -- I hope

15   it doesn't say that.

16   DR. FISHER: Do I read the sentence

17   starting on Line 752? "Such events include myocardial

18   infarction, stroke, as well as pulmonary embolism."

19   CHAIRPERSON PACKER: Life threatening

20   arrhythmia here is not nonsustained VT.   It is

21   supposed to mean sustained VT or VF.

22   DR. LIPICKY: Life threatening.

1   CHAIRPERSON PACKER: Life threatening, not

2   potentially life threatening. Life threatening.

3   DR. FISHER: Okay, but I mean there have

4   been studies where you reduce VT. How long is

5   sustained VT? With VF it's hard to argue against

6   that.

7   DR. THADANI: Thirty seconds --

8   DR. LIPICKY: Well, I think is what you're

9   saying, Lloyd, that that's an EKG finding and not a

10   clinical finding?

11   DR. FISHER: Well, that's the way I read

12   it, in part. Obviously I misunderstand it.

13   DR. LIPICKY: Did you mean that, Milton?

14   CHAIRPERSON PACKER: Maybe   the   word

15   "immediately life threatening" is --

16   DR. LIPICKY: But that's still an EKG

17   finding.

18   CHAIRPERSON PACKER: Well --

19   DR. FISHER: If it's VF I'll go with it.

20   DR. DiMARCO: You mean the arrhythmia

21   itself is life threatening at the time.

22   CHAIRPERSON PACKER: Yes.

1   DR. DiMARCO: Not that it portends future

2   risk.

3   CHAIRPERSON PACKER: That's right. That's

4   what I mean. How do you say that?

5   PARTICIPANT: Well, it depends. I mean,

6   it's sudden death, I suppose.

7   CHAIRPERSON PACKER: But they -- okay.

8   We'll be very specific. Okay. No problem. I've got

9   it.

10   One thing which we haven't discussed which

11   the guidelines talk about, before we go into analysis

12   -- we're still in Section 5.2 -- is whether the

13   analysis of -- there's a statement in the guidelines

14   that the best way of analyzing death is all cause

15   mortality.   That's   the   least   biased,   most

16   comprehensive approach.

17   The guideline -- and there's been lots of

18   discussions about this -- is less definitive about the

19   analysis of hospitalizations, and I just wanted to

20   talk about this for just a minute.

21   In many clinical trials, the analysis of

22   hospitalizations,   there   is   not   an   analysis   of

1   hospitalizations for any reason. It's a cause

2   specific analysis, whereas mortality tends to be death

3   for any reason.

4   And this guideline, and I want to

5   emphasize, has gone back and forth on this issue and

6   right now is worded in such a way as to try to make

7   both points of view happy and may, in fact, have

8   failed miserably in doing so.

9   But the guideline now states that one can

10   specify cause specific hospitalization as the

11   endpoint, but one needs to analyze all

12   hospitalizations regardless of cause in order to make

13   sure that a beneficial effect on a cause specific

14   hospitalization is not accompanied by an increase in

15   hospitalizations for other reason, given the

16   uncertainty in the classification process.

17   And that is slightly different than a

18   previous version of this document that actually had a

19   stated preference for all hospitalizations regardless

20   of cause, and in fact, I have noticed that in Section

21   5.2.4, Line 781, that a line remains from the old

22   version of this document, and that line says,

1   "Composite endpoints that include all events, death

2   and hospitalization for any reason are preferred over

3   cause specific composites." That is a holdover from

4   the previous version.

5   And I just wanted to get a sense from this

6   committee as to whether there is any preference for

7   cause specific or all cause hospitalization. The

8   issue here is not mortality. The issue is

9   hospitalization, and I specifically would like to ask

10 both John and Dan to address this because this comes

11 up all the time in arrythmia trials, all the time in

12 arrythmia trials, and in heart failure we have lived

13 a little bit of a dichotomous life in that we have

14 felt very comfortable saying that in arrythmia trials

15 it should be all cause, but in heart failure trials we

16 can do cause specific.

17   That may or may not be fair. So I really

18 would like both John and Dan to address this in a way

19 that helps advance the guidelines.

20   John?

21   DR. DiMARCO: Yeah. Having tried to

22 assign causes even though, you know, that wasn't the

1   primary endpoint, it is so difficult that you run into

2   problems that I think the trend is that you have to

3   look at all endpoints.

4   Now, could you possibly define some

5   endpoint, you know, if you're looking at people with

6   Class 1 symptoms or Class 2 symptoms and you're

7   looking at delay of progression? Do you have to count

8   everyone who goes into the hospital for, you know,

9   prostrate surgery or knee surgery or something like

10   that?

11   So you might say nonelective

12   hospitalizations, but I think that you're going to get

13   your most certain data if you look at all

14   hospitalizations simply because I can't tell the

15   difference between an admission for dyspnea from heart

16   failure, dyspnea for, you know, chronic obstructive

17   lung disease, and a pulmonary infection which

18   aggravates heart failure, admission for arrhythmia

19   which might cause heart failure or might be related to

20   worsening of heart failure. All of those things are

21   terrible.

22   And, you know, we tried to say, well,

1   let's look at cardiac mortality. Sure, if you're

2   looking at sick people, most of the events are

3   cardiac. If you're looking at people with Class 4

4   heart failure, most of the events are heart failure,

5   but I don't think you can really make the distinction

6   in a lot of cases, except for these elective surgical

7   procedures perhaps.

8   CHAIRPERSON PACKER: So your preference

9   would be?

10   DR. DiMARCO: All cause.

11   CHAIRPERSON PACKER: All cause mortality

12   plus all cause hospitalization?

13   DR. DiMARCO: Yes.

14   CHAIRPERSON PACKER: Dan.

15   DR. RODEN: I really don't have very much

16   to add, except that I continue to be troubled by the

17   whole idea of this combined endpoint that somehow

18   equates -- and "equates" is the wrong word -- death

19   and hospitalization as sort of a -- and maybe this

20   isn't the right time to talk about it or put the issue

21   on the table -- but you know, it seems to me that, you

22   know, one is a more serious endpoint than the other,

1   and the obvious rationale for using combined endpoints

2   is to keep the numbers involved in trials such as this

3   manageable.

4   I can see the arguments on both sides, but

5   I continue to be uncomfortable with composite

6   endpoints, particularly composite endpoints that

7   combined two or three or four different kinds of

8   endpoints, some of which are clearly much more serious

9   than others.

10   I really don't have anything to add to

11   what John said in terms of classification. You know,

12   he did it in some trials, but I've also sat on events

13   committees, and it becomes pretty pathetic when the

14   cause of death is assigned by a majority vote. You

15   know, people die for some reason and just because a

16   majority of the committee thinks one thing and a

17   minority thinks another doesn't make either side

18   right.

19   So I vote for or I would be inclined to

20   say total mortality certainly, and the hospitalization

21   issue, I think there must be a way to get : ide of, you

22   know, elective medial or, you k now, elective,

1   elective, you know, anterior cruciate ligament repairs

2   or something, but otherwise I think I'd go for total

3   hospitalizations.

4   CHAIRPERSON PACKER: Okay. I just want to

5   keep on going down the committee here because this is

6   such a controversial issue, and we keep on looking at

7   this in different ways, and I think that the one thing

8   which is very reassuring is that as far as I can tell

9   from the literature, every drug which has had an

10   effect on cause specific hospitalization has also had

11   an effect on all cause hospitalization.

12   The ones I can think of -- tell me if I'm

13   wrong -- dig., ACE inhibitors, and beta blockers have

14   all affected all cause hospitalization as well as --

15   the magnitude of the effect is different. Don't get

16   me wrong. The magnitude of the effect is much smaller

17   for all cause, but a significant effect has been seen

18   in databases on all cause as well as cause specific,

19   and that's a true statement.

20   Yes, that's true in the dig. trial, beta

21   blocker trial, and ACE inhibitor trials. The only

22   exception I know of is one trial which is the solve

1   (phonetic) prevention trial, prevention trial, which

2   technically one is -- but in both the solve treatment

3   trial, as well as the consensus study, all cause plus

4   all cause was statistically significant.

5   DR. DiMARCO: The only thing is is there

6   a problem if you have a large number of these

7   unrelated hospitalizations in the background in terms

8   of sizing the trial. I think that's the difficulty.

9   CHAIRPERSON PACKER: Yeah, and of course,

10   the sicker the patients, the less likely you are to

11   run into those because a lot of Class 4 patients don't

12   undergo orthopedic procedures.

13   DR. RODEN: And if they were to undergo an

14   orthopedic procedure, they'd be stuck in the hospital

15   because they have classical heart failure.

16   CHAIRPERSON PACKER: That's a problem.

17   Rob, any thoughts on this? I just want to

18   go down the --

19   DR. CALIFF: I've wavered on this quite a

20   bit. It's obvious that the most persuasive case is

21   always all cause/all cause. If you show you reduce --

22   again, the principle being that patients would rather,

1   in general, not be dead and they'd rather not be in

2   the hospital.   So from the Tom Fleming purely

3   empirical care about the patient instead of biology

4   point of view, that would be the best.

5   But I think there is a strong argument to

6   be made in the heart failure population that I agree

7   with all cause mortality because I don't think you can

8   really tell the cause of death and also because there

9   can be competing increasing in amount of way and

10   causes of death in other ways that you would not want

11   to discount.

12   But I think for the hospitalization case,

13   particularly the more you get away from Class 4 heart

14   failure, the argument that the true treatment effect

15   can   be   diluted   by   less   relevant   types   of

16   hospitalizations, minor things, et cetera, is a strong

17   one.

18   So I would be very much in favor of where

19   you think you can do it all cause/all cause, and as a

20   second preference, where it's the most sensible, heart

21   failure specific hospitalization, but still measuring

22   everything because you want to guard against accepting

1   However, we have to be sure to accept

2   perhaps all cause/all cause, but measure everything

3   and report everything because you can have

4   nonuniformity of therapy effect, and if the

5   distribution of hospitalizations is different in the

6   population in which the drug is to be applied than the

7   randomized sample, you can have some paradoxical and

8   dangerous findings.

9   CHAIRPERSON PACKER: Udho.

10   DR. THADANI: I think my preference is all

11   cause/all cause. Obviously mortality is not the

12   issue. Hospitalizations sometime get confounded.

13   Now, supposing you're using a drug, for

14   example, a beta blocker, in a patient who has got mild

15   COPD and he gets worsening. He's hospitalized because

16   of the drug. Is it related really to the therapy?

17   I mean, I buy John's point. You know,

18   operation is one thing, but I think this is the best

19   way to do it. Perhaps we should collect data,

20   cardiovascular or cardiopulmonary -- I don't know --

21   because patient, Class 4, gets some infection or

22   whatever because heart failure is worse.

1   So many not only several vascular,

2   cardiovascular and pulmonary, as opposed to others, I

3   think we are digging for small issues.

4   Another important issue, I think when you

5   combine the composite endpoint of mortality plus

6   hospitalization, I would like to make sure that the

7   mortality is not going in the wrong direction. So

8   when a patient is dead, he's dead. So you have to

9   make sure it is coming in the right direction.

10   It may not benefit it, but as long as we

11   are not getting more patients for the sake of less

12   hospitalization, I think they should be taken together

13   rather than dissecting the issue if you've got a

14   composite endpoint.

15   CHAIRPERSON PACKER: Bob?

16   DR. TEMPLE: The main reason for using all

17   cause as opposed to some subset is not that you can't

18   tell what the cause is. You can use an independent

19   committee to decide that and be sure that it won't

20   introduce a bias into the study. It may introduce

21   inaccuracies, but that's not your biggest problem.

22   The reason for counting them all is that

1   you're worried about effects that go the wrong way.

2   The luxury of using all cause mortality is

3   fine if most of the deaths are due to the underlying

4   disease you're talking about. In a very long trial

5   where people are dying of many other causes, you may

6   just make it impossible to discover what you want to

7   discover, and those are practical limitations that

8   need to be looked at.

9   Just as an example outside cardiovascular

10   medicine, if you thought you had a preventative

11   treatment for melanoma and insisted that you show an

12   improved survival, you'd never be able to do it

13   because it's not an important enough cause of death to

14   show up.

15   So you wouldn't design a trial that way.

16   You'd look for presence of melanoma, not survival.

17   The other thing is one of the reasons that

18   people use combined endpoints that seem to have

19   different weights of endpoints, which I think is a

20   problem, like death plus hospitalization, is that they

21   ⁻·eally want to look at hospitalization, but you don't

22   want to let them not count dead bodies because that's

1   even worse than hospitalization.

2   So it isn't that the two are of equal

3   weight.   They're not, but you've got an endpoint

4   that's going to be driven by the hospitalization, and

5   you don't want people to get away with having deaths.

6   CHAIRPERSON PACKER: Yeah, that latter

7   point, that last point is very important because Dan

8   had said that he didn't think that they were equally

9   weighted. I think that the guiding principle is that

10   the combined endpoint is more likely to reflect the

11   hospitalization, but hospitalization using a worst

12   rank analysis -- I hate to use that term -- but

13   hospitalization which includes an analysis of outcomes

14   worse than hospitalization so that one doesn't get

15   into the issue of competing risk.

16   Tom, is that a -- Tom, Dave, Lloyd, that's

17   okay?

18   Because, in fact, most analyses of death

19   and hospitalization that are timed to first event are

20   driven entirely by the hospitalization.

21   DR. FISHER: Of course, one way to reduce

22   hospitalization is to have a lot of early deaths.

1   CHAIRPERSON PACKER: Right.

2   DR. FISHER: Which doesn't seem so

3   wonderful.

4   CHAIRPERSON PACKER: Right, which is why

5   you do the combined analysis.

6   DR. TEMPLE: We'll come back to this in

7   5.3.2.

8   CHAIRPERSON PACKER: Okay. Jay?

9   DR. COHN: We may be mixing efficacy and

10   safety here because efficacy would be a reduction in

11   mortality and in hospitalization for the disease we're

12   treating. Safety would really relate to the potential

13   adverse effects on other causes for hospitalization.

14   And in the best of all worlds, if we want

15   to have a highly powered study, we would try to look

16   at   heart   failure   deaths   and   heart   failure

17   hospitalizations.

18   Now, we all know the problem with

19   separating out deaths and hospitalizations, but as Bob

20   has pointed out, yes, there will be inaccuracies if

21   you have an endpoint committee, but you can eliminate

22   bias, and I think that it is still possible to learn

1   something from cause specific hospitalizations

2   certainly and perhaps even cause specific deaths.

3   So I don't think we should just throw it

4   away and say, "Aw, we can't do it. Forget it." I

5   think under certain circumstances if you had an anti-

6   arrhythmic drug and you only thought it could work on

7   sudden death, I don't think it would be inappropriate

8   to power the study for a sudden death endpoint,

9   recognizing that there's going to be inaccuracies, but

10   having a committee charged to make that judgment with

11   as much evidence as they could.

12   And you would lose a lot by forcing

13   yourself to look at all cause mortality with a drug

14   which was only aimed at a very specific mechanism of

15   death.

16   CHAIRPERSON PACKER: Jay, I'm going to

17   take the Chairman's prerogative of not asking people

18   to respond to that because my sense is that -- I'm

19   grateful that your example is, in fact, not part of

20   the heart failure guidelines because my sense is it

21   would evoke a lot of comment that might, in fact,

22   disagree with what you just said.

1   DR. COHN: Well, I would hope so.

2   CHAIRPERSON PACKER: But my hope is that

3 that can be discussed at a time other than this

4 meeting, and so we can keep going.

5   Well, what I hear people saying is

6 actually pretty consistent, which is that there is a

7 preference for all cause hospitalization, plus all

8 cause mortality, but that no one would deny a

9 sponsor's right to specify all cause mortality plus a

10 cause specific hospitalization, and that such analyses

11 might, in fact, be useful and insightful, but we would

12 like to see the alternative analysis performed, as

13 well, in order to provide appropriate reassurance that

14 the prespecified analysis is not biased.

15   DR. LIPICKY: But I think it goes both

16 ways, right? You want to see both analyses.

17   CHAIRPERSON PACKER: You want to see both

18 analyses.

19   DR. LIPICKY: Cause specific and all

20 cause.

21   PARTICIPANT: One could be a primary

22 endpoint.

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1   CHAIRPERSON PACKER: That's right, and

2 whatever you specify as a primary endpoint, think

3 carefully about it and be prepared to justify it.

4   Let me just, before moving to analysis, I

5 just want to -- this document makes clear that the

6 analysis of long term outcome in patients when an

7 indication is being pursued for a long term treatment

8 -- this is an indication not for short term IV use,

9 but when an indication is being pursued for long term

10 treatment -- the guidelines makes clear, and this is

11 different compared to the previous guideline, that

12 sponsors need to evaluate the long term effects of the

13 drug on major events whether or not an indication for

14 a reduction in risk of those events is being pursued.

15   That is a new element of these guidelines.

16 It does not say you need to do a mortality trial in

17 every one. It says that you need to come up with an

18 estimate of the risk of the effect of treatment on the

19 risk of major events; that it can reasonably provide

20 a point estimate as to what the treatment effect is;

21 and that there is one element in the -- there's one

22 specific aspect of the document which is -- and I

1 apologize for this -- a little bit out of date. It is

2 Section 7.3.1, the third bullet. Oh, it's Line 1350.

3 That last sentence should be struck

4 because it is arbitrary, but the statement still

5 stands otherwise.

6 "It is important to delineate an effect of

7 drug on all cause mortality and combined risk of death

8 or hospitalization for any reason whether or not an

9 indication is being pursued, and such delineation

10 should be sufficiently precise that an adverse effect

11 of meaningful size can be detected."

12 And if that sounds sufficiently vague,

13 that's okay because attempts to define that more

14 precisely than that do not necessarily make the

15 situation better, but it is really, really important

16 from a safety point of view or from the assessment of

17 risk to benefit that the effect of a drug on major

18 events long term be an integral part of any drug

19 development program even if the indication being

20 pursued is symptomatic status change alone.

21 Bob.

22 DR. TEMPLE: I think I want to raise a

1   question I asked before. That certainly seems

2   reasonable for any class you're not familiar with. Do

3   you have a view yet on whether that's equally true for

4   a class of drugs where you're pretty sure you know the

5   answer, such as ACE inhibitors?

6   CHAIRPERSON PACKER: I can give you my own

7   personal view, and I would say that for ACE

8   inhibitors, if you can be persuaded -- this is lots of

9   ifs, ands, and buts, and one doesn't want to make this

10   too complicated -- but if you think it's an ACE

11   inhibitor, I don't think there's any reason to address

12   that in a class of drugs with an ACE inhibitor.

13   Things get a little bit more complicated

14   when drugs have multiple mechanisms of action, and

15   they get a little bit more complicated if the

16   mechanism is similar but not identical, for example,

17   A2 antagonists and ACE inhibitors.

18   DR. TEMPLE: I agree completely, but one

19   of the issues is how to work up a drug in the same

20   class as other drugs, and there you do have some

21   information.

22   CHAIRPERSON PACKER: Right. Barry.

1   DR. MASSIE: You may or may not want to

2   add another sentence at the end saying you want the

3   data you need to estimate the risk to benefit ratio,

4   and that information might include other information

5   about the same class of the drug or the information

6   that you would get about this drug or a combination of

7   the two probably in many cases, and that's the reason

8   for getting this point estimate.

9   DR. DiMARCO: Does that place an unfair

10   burden on the first drug to be approved, and then the

11   second drug can just jump on?

12   DR. LIPICKY: Yes.

13   CHAIRPERSON PACKER: But that's life.

14   PARTICIPANT: But they get the market --

15   DR. MASSIE: But also I don't think that

16   this committee would take two. It depends on how

17   robust the experience is with the two, but I think at

18   the end of captopril and analopril we were not ready

19   to say that all ACE inhibitors still did something.

20   It took a third and a fourth to really get us to that

21   point, and that's because I think the captopril

22   mortality experience was very small at that time.

1   Analopril was only consensus.

2   So it sort of depends how much is in the

3   first case.

4   PARTICIPANT: So you really need a very

5   strong class effect.

6   DR. LIPICKY: I would like to get just a

7   little bit of clarification of the word "long term"

8   here.   So if I had two, three month exercise tolerance

9   trials that you said were okay and I could exclude

10   fairly reasonable adverse effect on mortality, say, I

11   could say it wasn't for sure one and a half times that

12   of placebo; is that long term data?

13   CHAIRPERSON PACKER: I think there are two

14   separate   issues,   Ray,   and   the   document   tries   to

15   specifically address it.

16   The   reason   to   go   long   term   is   for   two

17   reasons.   One, if you go long term, you're more likely

18   to have an adequate number of events, and second is if

19   you   go   long   term,   you   might   find   effects   which   are

20   different than short term.

21   And so I think that the example that you

22   have demonstrated would not be adequate in a patient

1   population that would have few events at three months,

2   but might be adequate for a patient population that

3   was so sick that most people would be expected to be

4   dead at three months.

5   So that's why I think that it isn't so

6   much the numerical number of months of follow-up which

7   is important, but to make sure that the length of

8   follow-up is appropriate to the severity of disease

9   being evaluated.

10   DR. LIPICKY: Right, but that the duration

11   of follow-up is important. I guess I'd like to get a

12   feeling for what the documentation for that is. It

13   basically is milrinone and flosequinine and period?

14   CHAIRPERSON PACKER: No.

15   DR. LIPICKY: Or it is bunches?

16   CHAIRPERSON PACKER: In terms of adverse?

17   DR. LIPICKY: Yes, where the long term

18   outcome differs from the short term outcome.

19   CHAIRPERSON PACKER: The only example I

20   know of is flosequinine. Milrinone I'm not persuaded

21   is a very good example because at least in the

22   published literature there are no data that milrinone

1   produced short term benefits.

2   DR. LIPICKY: I see. So then the concern

3   over long term data is because of one drug and the

4   clinical trials from one drug?

5   CHAIRPERSON PACKER: Oh, I'm so sorry.

6   Maybe I should clarify this. The milrinone data is

7   relevant here in the sense that only long term did

8   they accumulate enough events in order to answer the

9   question.

10   If you curtailed the milrinone database at

11   two weeks or four weeks or eight weeks or three

12   months, you know, the trends may have been adverse,

13   but there was no P value. There was no clear signal.

14   So, again, that's why I emphasized there

15   are two reasons to go long term. One is adequacy of

16   events, and second is for adequacy of the duration of

17   therapy, matching the duration of therapy to the

18   natural history of the disease in the patients being

19   studied.

20   For example, six months might be more than

21   adequate in an IV ionotrope dependent patient

22   population, but would not be adequate for an

1   asymptomatic LV dysfunction.

2   DR. MASSIE: Maybe to amplify that a

3   little bit, I think this gets to the same point, is

4   that the types of patients that are enrolled in six

5   month, symptomatic, exercise, time limited experiences

6   differ markedly from the types of people who are

7   enrolled in our long term morbidity and mortality

8   studies. Usually they're Class 2. They can exercise.

9   They tend to be younger, and they tend to be very

10   different.

11   And you could actually get no hint about

12   how adverse a drug would be at the end of six months

13   not only because of the duration of the study or, as

14   Milton pointed out, the severity of the illness, but

15   you might get a different patient population.

16   Even in the milrinone experience, Class 3

17   didn't look bad. It took Class 4 patients to see how

18   bad things were.

19   DR. LIPICKY: But you've confused me a

20   little bit now because I was following you. I thought

21   this was all event rate driven, and if you had enough

22   events in the period of time that you studied the

1   patients to make some statement of that would fit the

2   criterion, that that was enough, but now you're saying

3   it's not event rate driven. It's somehow or another

4   clinically driven.

5   DR. MASSIE: Well, I think it should be a

6   little bit of both, that is to say, it depends on the

7   population. Certainly you need enough events to come

8   up with an estimate, but you could probably find a

9   population that might have events, but might not have

10 a discrepancy between the events and the placebo --

11 this is hypothetical -- and the active therapy because

12 they're not at risk for whatever it is that's toxic

13 about that drug at this stage of their disease.

14   DR. LIPICKY: Right. Okay.

15   DR. MASSIE: It's possible, but I think if

16 you really want to know about mortality, you do have

17 to have some time duration, and you have to have some

18 six people in it.

19   DR. THADANI: Also, I think probably the

20 sample size on exercise studies are very small. You

21 have 100 patients, 200 patients maybe.

22   DR. LIPICKY: You don't find anything with

1   100 patients. You have to have 800, 500.

2   DR. THADANI: No, but I mean if you look

3   at the flosequinine data base, maybe the total sample

4   size, 400, as opposed to exposing, say, 4,000

5   patients.

6   Say if you had a large exercise study,

7   say, six months or three months, and you have 3,000

8   patients in the study with different disease, then at

9   least you get a comfort level that you're not going in

10   the wrong direction.

11   So I think you could design studies which

12   could look at symptomatic improvement with a

13   reasonable follow-up, you know, whether three month,

14   six month, as long as the sample is large enough and

15   your events are not going in the wrong direction.

16   And the reason I think we run into trouble

17   even with flosequinine, it was going in the wrong

18   direction. Although exercise improved, there was a

19   noise, and you were not sure. So I think you can

20   reduce that noise by increasing the sample size, at

21   least from my perspective.

22   CHAIRPERSON PACKER: Rob.

1   DR. CALIFF: Milton, I presume in the

2   analysis part we're going to address some general

3   thoughts about how to deal with the less frequent but

4   more important endpoint trending in the wrong

5   direction?

6   CHAIRPERSON PACKER: We will make a point

7   of doing that.

8   DR. CALIFF: I think it's really

9   important.

10   CHAIRPERSON PACKER: Okay. Well, why

11   don't we move to analysis now?

12   Okay. The analysis section is divided

13   into or will be discussed in two main parts. One is

14   the designation of primary and secondary endpoints,

15   and the second is principle of analysis, and, Dave,

16   you're going to take primary and secondary endpoints.

17   DR. DeMETS: Well, I was going to confine

18   my comments to the section that I guess is labeled,

19   you know, 5.3, which is primarily on page 16.

20   First of all, I think what I think of an

21   analysis plan is that you have some detail sin the

22   protocol proper, but perhaps more details in an

1   appendix to the protocol, and at least what's not

2   clear from what's written here is exactly how much

3   detail one needs.

4   I recently reviewed protocols which are

5   pages and pages, including pages and pages of shell

6   tables which I don't particularly consider an analysis

7   plan, but nevertheless I'm thinking a few pages of

8   detail relative to the primary and secondary outcomes.

9   I also think that the analysis plan should

10   cover not just the primary and secondary, but also

11   some   statements   about   the   analysis   of   baseline

12   covariants, the compliance issue, as well as toxicity,

13   which comes later, not part of my charge.

14   I think Tom might get to this, but I want

15   to say that the intention to treat principle, of

16   course, is key to the analysis of the primary and

17   secondary   outcomes,   and   my   concern   about   this

18   principle, I endorse it, but I find lots of plans that

19   are look alike plans that are being promoted, for

20   example, referred to as being intention to treat when

21   they really mean if you took the drug.   As you

22   randomize and you took the drug, then you're in.

1   Those kind of variations seem to be

2 popping up, and people very sincerely believe they're

3 doing intention to treat. I don't think that's true.

4 So I think you need to be very careful about how you

5 define that in this document, and I think it is

6 defined clearly, but maybe it needs to be put in bold

7 letters.

8   So most of the things that are listed on

9 page 16, I think, I'm in favor of with a couple of

10 issues that I wanted to discuss in a little more

11 detail.

12   But before I do that, there is one area

13 that I don't think is discussed much at all, and

14 that's the issue of interim analysis for your primary

15 and secondary events. I mean trials of heart failure

16 generally have a monitoring process of some kind. I

17 don't see much discussion of that, and maybe it's

18 covered somewhere else in the general document that

19 the agency has, but I think that would be helpful.

20   And maybe we can get around to talking

21 about what maybe Rob was getting to, if things are

22 going in the wrong direction or going in different

1   directions.

2   But the specific things that I wanted to

3   raise, on page 16, of course, one needs to specify a

4   primary or a couple of primaries and a few

5   secondaries. We don't want to have a long list of

6   secondaries, which gets you, but where I begin to have

7   problems, for example, the Lines 805 and 806. Trials

8   that failed to preserve primary effect can't analyze

9   the secondary, and on the surface that seems true, but

10   it can get complicated.

11   Suppose your primary is a composite event

12   and your leading secondary is death. Does that mean

13   you ignore death just because it wasn't listed as a

14   primary?

15   I'm also not sure I would define a primary

16   as the one that you allocate alpha to in the secondary

17   as long as you don't allocate alpha to -- I mean,

18   that's true perhaps, but the primary is the one you

19   design your trial around and the one you believe you

20   want to have an effect on.

21   So the specific issue of the composite --

22   say your composite outcome is your primary and death

1   is your secondary. If you don't allocate -- if you

2   declare death to be your second primary, then you

3   would allocate alpha to it presumably. We can discuss

4   how much later.

5   But if you don't declare the secondary,

6   then you don't allocate any alpha according to this

7   definition, and I think it's a tough problem, but I

8   think it's one that I think you wrestle with in

9   several heart failure trials, as you know.

10   My preference would be to have -- if death

11 is the primary, then it's not such a problem because

12 a composite might be the secondary, and things follow

13 in a logical order, but if it's the other way around,

14 which is often the case, that the composite is your

15 primary, what you do about death, I think, needs to be

16 clarified, and I have my own personal preference on

17 that.

18   This issue of the composite and the

19 primary though also leads to a dilemma with respect to

20 intermonitoring, to get back to that, which I

21 commented briefly at the heart failure meetings a few

22 weeks ago.

1   If death is a primary, is our first

2   primary, and your composite is your second primary,

3   you allocate .04 to the first one and .01 to the

4   second, something. You monitor on your primary, and

5   if you get the result early, you quit. If you have a

6   harmful effect, you might quit.

7   That, while it's not simple, at least it's

8   more straightforward.

9   The other way around though, suppose the

10   composite is your first primary or your primary and

11   death is the secondary. In reality, in heart failure

12   trials you are going to probably monitor on mortality

13   because that's what you get immediately.

14   The other information, especially if it's

15   cause specific, hospitalization, let's say, comes in

16   later. It comes dragging in. Even if it's all cause

17   hospitalization, you still may not get it immediately.

18   So you wind up monitoring on mortality

19   much of the time, and yet your primary is something

20   else, and how to work out those details also gets

21   complicated.

22   The last issue I want to comment on is the

1   allocation of alpha itself. I guess I'd make a

2   sidebar here and make an appeal that if we use the

3   term "spending alpha," what we really mean by that is

4   repeatedly testing on an outcome through the course of

5   the trial interim analysis part, and choose some other

6   term like "allocation of alpha" when we have more than

7   one outcome because these are different issues. They

8   are not totally unrelated, but they are still

9   different issues.

10   If we're ever going to talk about the

11   issue of allocation of alpha, I don't think it's

12   necessarily the right thing to do to have a composite

13   which is death plus something and death as the two

14   outcomes and divide alpha by two because you have two

15   outcomes. Those are highly correlated, and depending

16   on the mixture of death in that composite, you might

17   adjust differently.

18   So the issue of allocation of alpha, I

19   think, is more complicated than just dividing by the

20   number of outcomes you happen to declare as primaries.

21   So I think that's sort of a short version

22   of what I have to say, other than the issue of sample

size, which also appears in this section. I've used

sample size as sort of a part of the design section,

and while you definitely need to have it here in the

kind of detail that's necessary, I would hope that it

would be more in the design section and not something

that people think about at the time of analysis.

CHAIRPERSON PACKER: Okay. Why don't we

go on directly to Tom's comments, and we can discuss

everything in a unified fashion?

Tom.

DR. FLEMING: I'll just use a single

transparency here.

The principles of analysis, Section 5.3.2,

relate to a couple of concepts. One is the intention

to treat analysis, and the second relates to handling

of dropouts or missing information.

I'm largely in agreement with the essence

of what's in the document on these two pages. The

intention to treat analysis provides two major

clinical or two major scientific benefits. One is

that it preserves the integrity of randomization.

Randomization gives us comparability, but

1   we only retain that comparability if we continue to

2   follow all patients to the intended clinical endpoint.

3   If we have patients who are lost to follow-up, if we

4   have patients who become noncompliant and we lose the

5   data on the clinical endpoint, if we have patients who

6   take concomitant meds. and we stop following them for

7   that reason to the clinical endpoint, those are

8   reasons that could well or factors that could well

9   differ between the intervention and control arms, and

10   we lose the integrity of randomization.

11   It's also, I believe, the most clinically

12   relevant analysis in that unless we can tell in

13   advance who's going to be noncompliant, who's going to

14   be unable to tolerate a therapy, what we wish to know

15   is globally what is the outcome. That's an analysis

16   that includes all people.

17   So the goal then is to follow all patients

18   for the clinical endpoint, including those patients

19   who for some reason would discontinue early.

20   Now, the second part of the document and

21   this section deals with what approaches you would take

22   if you haven't followed all people, and I think it

1   appropriately addresses concerns that arise with the

2   completer's analysis. I won't add to that.

3   It also points out the last observation

4   carried forward also has the same problems as the

5   completer analysis, but also suffers in that it

6   commingles early and late effects, which I not only

7   agree with, but I would add to that it also commingles

8   natural history changes over time because if you're

9   carrying forward, for example, in the placebo arm and

10   natural history is changing over time and you're

11   wanting to assess at a later point in time, you're

12   carrying forward early natural history assessments to

13   later points in time.

14   The worst rank assignment is one that I

15   want to spend a little bit of time talking about

16   because there's a setting in which I think it makes

17   sense. I call "okay for death," although more

18   generally I would say it's okay in the context that is

19   stated here, which is for outcomes that are of major

20   importance, but it's not okay for missing information.

21   So let me try to be explicit with a

22   trivial example. Suppose we're comparing placebo with

1   treatment, and we have a study with five patients, and

2   suppose on the placebo arm we're going to have three

3   patients die, one who will be alive with symptoms and

4   who will be alive with good quality of life.

5   Suppose the treatment yields in essence in

6   five other patients. The patient who is alive, this

7   patient is correspondingly alive. This patient is

8   correspondingly alive with symptoms, but the three

9   patients who would have died, they would all survive

10   now, two with symptoms and one without symptoms.

11   So clearly this is a treatment that

12   provides important clinical benefit. In terms of

13   overall survivorship, it improves survival from 40

14   percent to 100 percent, but it's acknowledged that

15   there's more to it than survivorship. So maybe we're

16   looking at not only surviving, but surviving with good

17   quality of life, symptom free survivorship, in which

18   case the placebo would have only 20 percent of people

19   alive free of symptoms, whereas the treatment arm

20   would have 40 percent of people alive free of

21   ·ymptoms.

22   On the other hand, if we said those people

1   who die we're going to just leave out of our analysis,

2   we're going to condition on survivorship and analyze

3   the data conditioning only on those people who are

4   alive to see whether or not the treatment was

5   effective.

6   We find in the placebo arm that of those

7   survivors, 50 percent are free of symptoms, whereas on

8   the treatment arm of the survivors, only 40 percent

9   are free of symptoms.

10   So if we don't use this approach here of

11   assigning a worst score to those people that have a

12   bad thing to death and simply eliminate them from the

13   analysis, we would get the very misleading conclusion

14   that this treatment is ineffective because there are

15   fewer percent, 40 percent, of the survivors that are

16   free of symptoms than on the control arm, clearly a

17   very misleading conclusion since this treatment

18   clearly is effective.

19   So the essence of the conclusion here is

20   not only is it okay in my view when you have -- let's

21   say you're looking at a study where the primary

22   endpoint is symptom improvement. Not only is it okay

1   to assign those people that have a serious major

2   consequence, such as death, the worst score.   I

3   believe it's imperative in order to have a readily

4   interpretable conclusion.

5   So essentially what I think we are

6   required to do when we're looking at symptoms is to

7   look at the endpoint symptom free survival.

8   Now, on the other hand, suppose what we're

9   talking about is not events happening to these people

10   that are deaths, but rather events or consequences to

11   these people that lead to missing information. If we

12   assign the worst possible rank when these three people

13   simply have missing information, it could certainly be

14   a biased analysis because it's entirely unclear

15   whether the people who are missing are like those

16   people who aren't missing or unlike those people who

17   aren't missing.

18   And a lot of times we get the impression

19   the worst rank assignment must be a conservative

20   analysis. It's a worst case analysis. That's not the

21   worst case analysis.

22   In this case, if we assigned a worst rank

1   analysis and these three people on placebo are simply

2   missing, we will get the impression there's a big

3   difference. Treatment is much better than placebo if

4   you assign these three people a worst rank analysis,

5   when in reality these three people may be doing just

6   fine. They may have just become lost to follow-up.

7   So the bottom line is this worst rank

8   assignment is not only okay. I think it's imperative

9   when you have data, quote, unquote, missing because of

10   death or bad event. In fact, in my view it's not

11   missing at all. It's there and it's a bad outcome.

12   But when you truly have missing

13   information, this approach is as flawed as the

14   completers analysis and the last observation carried

15   forward, i.e., they are all flawed, and the only real

16   positive solution is making every possible reasonable

17   attempt to keep missing information to a minimum.

18   DR. THADANI: What do you do if

19   information is missing though? I know your trial is

20   over, and you can count the bodies or you can look at

21   the death registry and they're still alive, and you're

22   saying it's biased. What do you do with it?

1   DR. FLEMING: Well, certainly to an extent

2   it will be a reality that some "missingness" is going

3   to occur, and if we're able to keep that "missingness"

4   to levels of one percent or below, for example, of

5   course, then the amount of "missingness" -- the impact

6   it will have depends also on how frequent the events

7   are.

8   In a trial in which 20 percent of people

9   have events, one percent with missing data will be

10   less likely to impact the integrity of that analysis

11   than in a study that has only one percent of people

12   having events where one percent are also missing

13   information.

14   So the bottom line is if there's missing

15   information, it compromises the integrity of the

16   analysis or the reliability of the conclusion.

17   However, if the amount of "missingness" is very small

18   relative to the amount of events that we have, then

19   it's likely that that "missingness" will have a

20   relatively small effect.

21   DR. THADANI: Say, for example, in an

22   exercise database, he didn't die, but he got

1   hospitalized for worsening failure. Then, you know,

2   you could give him a zero score, too, because he was

3   not able to exercise and he became Class 2 to 4.

4   Can you apply that? As long as you've got

5   some information on the patient, it depends on what

6   endpoint you're looking at.

7   DR. FLEMING: Well, according to the

8   document as it currently reads, I think it handles

9   that situation. It says worse rank assignment. "In

10   this approach, patients who experience clinical events

11   of major importance are assigned the worst rank."

12   For the argument that I was giving, I not

13   only accept that. I strongly endorse that approach,

14   and you were saying, I thought, if you were looking at

15   symptoms and someone becomes hospitalized, I think one

16   could argue that hospitalization is a bad event, and

17   in fact, possibly worse event than the symptom outcome

18   that you're looking at.

19   What we're trying to achieve here is a

20   good outcome, i.e., a patient who is alive and symptom

21   free or alive and symptom and hospital free and so

22   somebody who has a bad outcome because of death or

1   hospitalization legitimately can be given a worst rank

2   because they clearly have had a bad outcome.

3   The problem is when someone is missing

4   information not because of death or hospitalization,

5   but doesn't get your symptom assessment because they

6   never came back, and if this happens, on rare occasion

7   it's not going to have a substantial impact on your

8   analysis, but if it happens with considerable

9   frequency, then all of these approaches that are laid

10   out here, worst rank analysis, observation carry

11   forward, and completers analysis, will all give you a

12   sense, will all be analyses that you can do to get a

13   sense of what these results or what the effect is, but

14   the reliability of the conclusions will be less.

15   DR. THADANI: And, Dr. DeMets, you

16   mentioned that the primary composite endpoint is

17   negative, but for some reason, say, the death rate

18   goes down. Yet the event rate is low and you can't be

19   confident that if you do the next trial it will go the

20   right way.

21   So I know you say you can't ignore it, but

22   how confident can you feel that the trial is negative

1   on the composite endpoint, but the death which was

2   secondary endpoint, there's a positive trend?

3   That really at least as a clinician I'm

4   asking you is there enough for approval. Are you

5   really mandating there's a trend and you have to go

6   large modality power with either enough event rate or

7   power to give you approval for that indication and not

8   just say it produces death because of this?

9   DR. DeMETS: Well, my assumption was that

10   you're only interested in this discussion if the

11   secondary endpoint of death is convincing. I would

12   understand a trend wouldn't be sufficient in my mind.

13   DR. CALIFF: Well, maybe, David, to carry

14   that a little further, if the primary endpoint is flat

15   out negative --

16   DR. DeMETS: By negative do you mean

17   neutral or --

18   DR. CALIFF: Yeah, neutral.

19   DR. DeMETS: Okay.

20   DR. CALIFF: How convincing would a

21   mortality result need to be to get your attention? I

22   mean I know the most conservative view would be if it

1   wasn't the primary endpoint, and the primary endpoint

2   was negative, you've, quote, spent all of your alpha.

3   It's over, and you've raised an interesting

4   hypothesis.

5   The most liberal view, I guess, would be

6   that since death is such an overwhelmingly important

7   clinical endpoint, that if it was conventionally

8   significant as if it were the primary endpoint, then

9   that would be convincing.

10   How does the statistician advise weighing

11   those things?

12   DR. DeMETS: Well, the first thing is

13   something you decide, you know, how you allocated your

14   alpha.   If you didn't allocate anything, if it was

15   just strictly a primary and a second -- if you

16   allocated alpha, you have some criteria to judge that

17   on.   I mean, you may have made a stupid allocation,

18   but at least you made some decision.

19   If you haven't allocated alpha, the

20   question is, you know, do you just ignore death

21   altogether, and I can tell you trials in pulmonary

22   disease, which I used to work in, that in fact

1   happened, and you know, I think we used common sense

2   and decided that mortality was -- I mean why are you

3   worried about this?

4   You're worried about that you'll dredge up

5   some secondary outcome by chance alone that you just

6   happened to stumble into, but I don't think, for

7   example, death is just one of the many secondary

8   outcomes.

9   DR. THADANI: But that happened in the

10   resterone (phonetic) trial. If you look at the first

11   trial which came out in the New England Journal of

12   Medicine, there was a 16 milligram dose, was 54

13   percent reduction in mortality. Cardiology was having

14   an outcry the FDA didn't approve the drug because

15   these patients could be all alive, and yet the big

16   trial which was powered to count a lot more deaths

17   went totally wrong direction.

18   So you know, you are saying it never

19   happened or just it's just a chance or something

20   happened in that trial. Even when we counted the

21   bodies they were wrong.

22   DR. DeMETS: Well, first of all, those are

1   tow separate trials. So I'm not sure that it's

2   relevant to the problem I posed. I mean --

3   DR. THADANI: It happened that the

4   mortality was --

5   CHAIRPERSON PACKER: Udho, that's not a

6   good example because, in fact, in that trial that you

7   referred to, the primary endpoint was, in fact,

8   achieved as well as the secondary endpoint of

9   mortality. The problem was that for all sorts of

10   reasons, maybe including the small number of events,

11   it couldn't be replicated, and in fact, went in the

12   opposite direction, and who knows what went on?

13   It's not a good example for the principle

14   being discussed.

15   DR. FISHER: It was also the dose response

16   pattern.

17   CHAIRPERSON PACKER: Yeah, it was.

18   DR. THADANI: But that's why I said the

19   number of the events. That was my initial question,

20   how many rents you'd need to be confident that you're

21   going to be positive. Are you going to be --

22   CHAIRPERSON PACKER: Yeah, it's a

1   different question where you allocate your alpha.

2   DR. DeMETS: The one appeal I was making,

3   I don't think you should just divide alpha by two

4   because you have a primary and a composite and death

5   as your two outcomes. You've got to adjust based on

6   the correlation that's implicit.

7   DR. MASSIE: Do you get more than .05

8   worth because the two are so highly correlated?

9   I mean, it seems to me because they're so

10   highly correlated it shouldn't be .04 and .01 or

11   something that adds up to .05, but it should be

12   something that adds up to more than .05. Is that true

13   or not?

14   DR. MOYE: It depends on the degree of

15   correlation, but if you have two endpoints and let's

16   say they both absurdly are perfectly correlated, you

17   know, and Event A happens in a person and Event B

18   happens as well and if A doesn't happen, then B

19   doesn't happen. Then you look at the alpha for the

20   two experiments is the same -- sorry -- for the two

21   endpoints is the same as the alpha for one.

22   So you get --

1   DR. MASSIE: But the importance might be

2   that 30 percent of the combined endpoint would be

3   death. So there's that much correlation.

4   DR. MOYE: Well, yeah, there's some

5   correlation, but the trick is figuring out exactly how

6   much correlation there is, but you get substantial

7   alpha savings.

8   And to go back to Dave's other point about

9   are there circumstances when you can have a trial

10   which is negative for the primary endpoint and

11   positive for the secondary endpoint, I think if you

12   prospectively specify your alpha allocation -- I won't

13   use "spendings" -- the alpha allocation, then I think

14   that that's not a problem.

15   If you have a primary endpoint that you

16   allocate .03 to and it comes in at .3 so that you're

17   way off, and you allocated .02 to the secondary

18   endpoint and you came in at .001, then there's no

19   problem with -- from my point of view, there's no

20   problem with calling that trial positive. You

21   still --

22   DR. CALIFF: Well, I think there's

1   universal agreement on that. The question is what if

2   you didn't.

3   DR. MOYE: But if you don't allocate, if

4   you don't allocate, then, you know, every decision you

5   make has a down side. If somebody who is, I guess,

6   alpha hypersensitive, would say that -- I mean, I

7   recognize that there are going to be some times that

8   I'm going to throw out the results of the baby with

9   this bath water of alpha hypersensitivity, and I

10   recognize that.

11   But it seems to me the alternative is to

12   open the door for investigators, having announced with

13   great fanfare what their primary endpoint is, and the

14   primary endpoint is really the axis around which the

15   trial revolves. You spend a great deal of care and

16   deliberation working that primary endpoint up, making

17   sure that you measure it with a good degree of

18   accuracy and precision. I mean, that's chosen not

19   randomly, but it's chosen because that's were you

20   believe the effect is going to be.

21   Now, if you've done that and you're wrong

22   about that, I disagree with the concept of kind of

pushing that primary endpoint which was held in high regard into the scientific back water while you rush up a secondary endpoint which perhaps you didn't anticipate.

I mean, I agree that this notion of primary and secondary endpoint is somewhat artificial, but it requires investigators to make decisions prospectively about where they think they're going to see the event.

If you decide to go by the secondary endpoint finding when you didn't prespecify alpha, then you run the risk of having by chance obtained a sample where your primary endpoint was negative, your secondary endpoint was positive when, in fact, that really doesn't reflect what's going on in the population, and from my point of view, that's what's really paramount here, what's happening in the population.

CHAIRPERSON PACKER: I don't want this to evolve into a discussion of how one spends alpha.

DR. MOYE: Well, it's too late for that.

DR. FISHER: Contrary to what you think,

1   Milt, I'm not going to respond to that other than to

2   say the February issue of <u>Controlled Clinical Trials</u>

3   will have a long discussion about this.

4   I want to get back because of the limited

5   time and be sure --

6   CHAIRPERSON PACKER: I'm sorry, Lloyd.

7   There was one part of this alpha thing that I did want

8   to -- and, you know, whether or not one's alpha

9   receptors are up regulated or not --

10   (Laughter.)

11   CHAIRPERSON PACKER: -- I just want to

12   make sure that I understand one thing because what we

13   are seeing now, and the examples which have preceded

14   us on the alpha spending or the alpha allocation issue

15   may or may not be good examples, there is one kind of

16   example that we're seeing a lot of now, and I wanted

17   to get people's comments on.

18   We are seeing trials where the primary --

19   these are long term, big, multi-center, large scale

20   trials. The primary endpoint is a combined endpoint,

21   and let us not go into reasons why it's a combined

22   endpoint.   It is, and it includes mortality and

1   hospitalization, and let's not talk about whether it's

2   cause specific hospitalization or not.

3   The secondary endpoint or one of the

4   secondary endpoints, but just for simplicity's sake,

5   let's say there's only one secondary endpoint that

6   happened to be mortality, and the two are going to be

7   correlated. They're not going to be correlated, Lem,

8   at 1.0. They're not going to be perfectly correlated,

9   but they are going to be correlated.

10   So the primary endpoint is a combined

11   endpoint of death and hospitalization. The secondary

12   endpoint, only one, is mortality alone, and there is

13   some correlation between the two.

14   To what degree does a sponsor need to

15   assign alpha to the secondary endpoint of all cause

16   mortality, realizing that the sponsor has already

17   recognized mortality is very important because it's a

18   component of the primary combined endpoint?

19   There's already a recognition that the

20   combined endpoint is going to be most easily

21   interpreted if the components go in the right

22   direction, the same direction.

1   Does the sponsor have to waste any

2   allocation of alpha on the mortality in a design of

3   that nature? Because we are going to see more and

4   more trials like that because there is a tendency to

5   consider those trials to be more reasonably sized than

6   trials in which the all cause mortality would be the

7   primary and the combined endpoint would be the

8   secondary.

9   So since this is such an increasingly

10   common situation for outcome study, I'd like to hear

11   some just brief discussion as to how sponsors should

12   deal with this situation, and what I like about this

13   example is it goes away from the extreme examples that

14   everyone can actually agree with.

15   This is an example where, you know,

16   there's truly a middle point being discussed, and the

17   question is: does the sponsor have to assign any

18   alpha to the secondary endpoint of all cause

19   mortality, or is it just assumed that if they went on

20   all cause mortality -- and we're saying Udho -- we're

21   going to address Udho's concerns -- let's say there

22   are 500 deaths. It's not an issue of the number of

1   events.

2   The question is whether alpha allocation

3   here is helpful. Comments?

4   DR. LIPICKY: I think you have to specify

5   just a little bit more, and that is is the protocol

6   the expectations of the people doing the study that

7   this is the equivalent of two primary endpoints in the

8   sense that if they win on either one, that means that

9   there is a positive -- a finding that must have

10   attention paid to it.

11   So it's not primary and secondary. It is

12   do they carry equivalent weight.

13   CHAIRPERSON PACKER: Yeah, I think that

14   the reason why this would be -- I'm trying to make the

15   question actually more interesting than the automatic,

16   well, gee, you know, they achieved the primary .01.

17   I'm just assuming that, and they achieved mortality at

18   .01, but that wouldn't be a very interesting question

19   because everyone would agree how that should be

20   interpreted.

21   The more important question is they

22   achieved an effect on the combined endpoint of .1, but

1   hit mortality at .01.   Mortality is the secondary

2   endpoint.

3   DR. LIPICKY: Well, I don't think it makes

4   any difference whether it's primary or secondary.

5   CHAIRPERSON PACKER: That's what I wanted

6   to know.   That's what I want to know.

7   DR. LIPICKY: What conclusion do you want

8   to draw?

9   CHAIRPERSON PACKER: What conclusion do

10 you want to draw? What conclusion can you draw?

11   DR. LIPICKY: Right, and is the conclusion

12 you can draw dependent upon how the endpoints were

13 designated?

14   CHAIRPERSON PACKER: Right.   Does it

15 depend on how the endpoints were designated?

16   DR. LIPICKY: Right.

17   CHAIRPERSON PACKER: If it doesn't, then

18 a lot of people are wasting a lot of mental energy.

19   DR. LIPICKY: Correct.

20   CHAIRPERSON PACKER: Right.

21   DR. MASSIE: I just want to go back to

22 what   I   raised   because   I   think   this   is   the

1 nonstatistical view. They're correlated. You deserve

2 more than .05. Put them both primary and say .05, we

3 hit it for the combined, and .01, we hit it for

4 mortality.

5 DR. MOYE: I guess I would say that if you

6 have .05 to allocate, I would, number one, advocate

7 that alpha be allocated for both the primary endpoint

8 and for the secondary endpoint of total mortality.

9 And also, since they are dependent, then

10 the alpha I allocate doesn't have to add to .05

11 because of the dependency. I don't know exactly how

12 the numbers work out. It depends on the dependency,

13 but you may be able to allocate .035 for the primary

14 and something like .03 or .035 for the total

15 mortality, and because of the dependency, the overall

16 alpha expended would be .05.

17 CHAIRPERSON PACKER: Lloyd and Tom and

18 Dave, yes.

19 DR. FISHER: Yeah. Number one,

20 statisticians can't take into account the dependency

21 and adjust for that in an appropriate way. The

22 problem we have here is normally if someone moved to

1   a composite endpoint, there is little expectation you

2   have enough deaths to pin things down. That probably

3   would have been your primary endpoint.

4   If that's the case, people often say, "Oh,

5   well, let's save a little alpha. For mortality we

6   don't expect to get it. We don't want to lose my

7   power, so we're going to put a very small amount on

8   it."

9   Here's something that had almost no power

10   to start with, and you get a really small alpha. The

11   power is just, you know, just down the tubes.

12   So I think it makes sense not to allocate

13   alpha, and as recent history showed, by and large, I

14   agree with Lem, but in that case it would take an

15   extremely strong finding, in fact, a P less than

16   .00125, which is somewhere else in these guidelines as

17   I recall.

18   CHAIRPERSON   PACKER: Actually   the

19   guidelines just -- yeah. We'll talk about that later.

20   DR. FISHER: That's if it's a design

21   primary endpoint because you want to do with one trial

22   with an equivalent level of proof.

1   Another issue that comes up is if your

2   trial is, let's say, at the .05 level or whatever

3   level, if the combined endpoint is there, but not the

4   serious irreversible part of the combined endpoint,

5   then you can ethnically do more trials easily. So

6   that there is a difference depending upon whether you

7   just make your combined endpoint or whether you make

8   both.

9   To me the much more interesting question

10 which relates to partly what Rob brought up is you

11 meet your combined endpoint, but there's a mild trend

12 in the wrong direction for mortality, but you have

13 enough hospitalizations, say, so that the composite

14 endpoint is there. That to me brings up -- well, it

15 mixes efficacy and safety, I guess -- but that brings

16 up very difficult issues.

17   CHAIRPERSON PACKER: You see, Lloyd,

18 although I agree with what you said in terms of, gee,

19 if they thought they were adequately powered for

20 mortality, they would specify that as a primary, but

21 not necessarily because it could be that a sponsor

22 wants to put all of its resources into one trial

1   sufficient so that they will try to achieve an effect

2   that is .00125 on the primary.

3   Therefore, power -- put an enormous power

4   in the primary, but going for a conventional level of

5   significance for mortality alone. Therefore, they're

6   actually doing a mortality trial, but specifying the

7   combined endpoint as the primary because the trial

8   would be able to achieve a very persuasive effect on

9   the combined.

10   DR. FISHER: Right, and in that case --

11   and let's say they met the .05. If you put it as a

12   secondary, normally we don't adjust because they

13   already have a hurdle, but you don't penalize the

14   people for passing that hurdle.

15   In that case, if I were the agency, I

16   would not let the people advertise mortality benefit,

17   but obviously the community would know it was there

18   and think it was likely.

19   DR. LIPICKY: Maybe I'm confused. This

20   isn't a primary/secondary endpoint you're talking

21   about. You're talking about somebody specifies a

22   combined endpoint, and there is always a problem with

1   a combined endpoint in that there's more than one

2   thing that is represented.

3   DR. FISHER: Right.   What I've been

4   talking about is the primary is the combined endpoint.

5   DR. LIPICKY: Oh, but it doesn't matter

6   whether it's primary or secondary. If one declares an

7   endpoint and invests all of the alpha of the trial in

8   that endpoint, it is primary.

9   DR. FISHER: Right.

10   DR. LIPICKY: If one has two endpoints,

11   whether one of them is in the combined or not, and

12   invests some alpha in a part of the combined endpoint,

13   they have two endpoints.

14   DR. FISHER: Two primary endpoints.

15   DR. LIPICKY: It doesn't matter whether

16   you call it primary or secondary.

17   DR. FISHER: Normally --

18   DR. LIPICKY: The   designation   is

19   irrelevant I would assert.

20   DR. FISHER: Well, maybe we should stop

21   using the term "primary" and "secondary" and just talk

22   about whether --

1   DR. LIPICKY: I agree with --

2   DR. FISHER: -- where we put our alpha.

3   DR. LIPICKY: I agree with that 100

4   percent.

5   DR. FISHER: But as far as I can tell, and

6   I don't know an exception, normally if something has

7   some alpha attached to it, it would be listed as a

8   primary endpoint.

9   DR. LIPICKY: Well, but that's just a

10   semantic thing. Conceptually I don't think it has any

11   merit.

12   CHAIRPERSON PACKER: Okay. Lloyd, do you

13   want to -- oh, I'm sorry. Bob.

14   DR. TEMPLE: Well, there are other

15   arrangements. I associate these with Gary Cook, but

16   that's probably just me, where you say, "I have to win

17   on my primary endpoint and then I'm interested in

18   other things if I do," where I think you were just

19   addressing that case, where you actually don't pay any

20   price at all because it wouldn't stand on its own.

21   You don't get to look at the mortality until you win

22   on the combined.

1   So that's sort of a different case, right.

2   CHAIRPERSON PACKER: Okay.   Lloyd, you

3   were going to bring up other issues.

4   DR. FISHER: No, I think Dave and Tom

5   were --

6   CHAIRPERSON PACKER: Oh, I'm sorry. Dave.

7   DR. DeMETS: Well, the reason I brought it

8   up is that the current document makes a passing

9   comment on the allocation of alpha, but isn't really

10   specific enough, I think, to guide us in what I think

11   is one of the more challenging issues at least in

12   heart failure trials.

13   What we have is this continuation of a

14   composite plus death as two outcomes, one primary and

15   one secondary. I think there are ways we can avoid

16   having to divide alpha by two. As I said, you take

17   into account the correlations.

18   But if you're not careful about this, you

19   get into some very awkward situations, especially for

20   monitoring trials and trying to come up with something

21   that's definitive and yet consistent.

22   DR. MASSIE: Let me just raise another

1 variation because I think it's also becoming as common

2 as this combined as the primary or as the major and

3 the one component as the second part of the major, I

4 guess, and which is really in -- maybe a best example

5 might be an Australia-New Zealand type of carvatelol

6 trial where because you want a large number of

7 patients, you may use them to look at two points in

8 time at two different, but potentially very related

9 things.

10 You're going to want to look at six months

11 to see how the patient is doing, a more symptomatic

12 endpoint, but it might be a composite that include

13 hospitalization and death as well, and then you want

14 to look long term for mortality.

15 To me it's almost the same example as what

16 we're talking about, except you're looking at two

17 points in time, and I guess what I would toss out as

18 a balloon is could you again, because of the

19 correlation of the two endpoints, could you do the

20 same type of arrangement? Assign your .05 to the six

21 month look, and then two years later when you're

22 looking at total mortality, which again probably makes

1   up a certain part of the early look if you specified

2   it that way, have .01 as well or Lem was more

3   generous. I think it was .035 and .03.

4   You know, it seems to me as long as you're

5   doing something reasonable, it's probably -- if you

6   put it in the protocol and it's reasonable and

7   everybody agrees to that, you know, you have as good

8   a bet at how to handle the correlation as any other

9   mathematical formula.

10   DR. FISHER: Just a technical point. I

11   don't agree that just because you put in the protocol

12   and it seems reasonable to start with that you can do

13   it that way. Once you have your data, there's

14   something called the randomization test where you can

15   adjust appropriately for the actual observed

16   correlation so that if the data, in fact, were not

17   correlated at all, you would pay an appropriate

18   penalty.

19   So I don't think it's enough to say,

20   "Well, we think this is going to be highly correlated.

21   So this one is going to be .04 and this one is going

22   to be .04."

1   DR. MASSIE: Okay. Yeah, I didn't know

2   that there was a good way to do it. If there's a good

3   way to do it --

4   DR. FISHER: Yeah, you can actually adjust

5   for that appropriately once you have the ratio of how

6   you're going to spend your alpha.

7   DR. MASSIE: But if you had 20 percent of

8   one endpoint events are part of the other endpoint

9   events or something --

10   DR. FISHER: Right, but there's a way of

11   adjusting that does preserve the Type 1 error rate and

12   sets it at the correct level.

13   DR. MASSIE: So is that another model that

14   one can follow?

15   DR. RODEN: How is that different from two

16   looks?

17   DR. MASSIE: They are different endpoints

18   because they're at a different point in time, and

19   maybe they have different components. The earlier one

20   might include -- well, just to give examples that we

21   know what happened -- death and hospitalization and

22   clinical status like is outlined in this protocol here

1   as early symptoms, and so everybody counts early.

2   DR. FLEMING: They're different types of

3   multiple testing. What you're referring to are two

4   different analyses at chronological periods of time.

5   What Barry's talking about are two different analyses

6   at different points past time zero, early treatment

7   effects after initiation of treatment versus --

8   DR. FISHER: And different endpoints.

9   DR. FLEMING: -- later treatment effects

10   after initiation of treatment.

11   DR. TEMPLE: But in that case would you

12   have to win at the early look?

13   DR. MASSIE: Well, that's the question.

14   DR. FLEMING: It depends on what you

15   define your criterion to be.

16   DR. TEMPLE: If you did, if you had to win

17   in the early look, then you've got one of these

18   situations where you don't even get to the last one

19   unless you've won on the first. It might not have to

20   pay anything.

21   DR. FLEMING: Well, not only do you not

22   pay something. Essentially now you're having to hit

1   on two, and hence you're able to be less conservative

2   because you're having to hit on tow.

3   DR. FISHER: Well, now, if you're --

4   that's a different statement. Whether you declare

5   success if you meet one of the two or whether you have

6   to hit two, and the procedures are different, but in

7   each case it can be adjusted for --

8   DR. MASSIE: Well, if you have to hit --

9   it's not an interesting question if you say you have

10   to hit two because then there's no question. The

11   question is what if you happen to only hit on the

12   early one but not the later or vice versa, but you

13   know, again, it's this concept of alpha allocation

14   with correlation between the two endpoints.

15   DR. FLEMING: All of these, everything

16   you're referring to are different variations to

17   multiple testing that can occur from multiple time

18   points on an endpoint, multiple endpoints, multiple

19   test statistics, subset analyses, secondary endpoints.

20   All of these things are multiple endpoints.

21   And what I would argue is the overall

22   assessment of efficacy requires a global evaluation of

1   all relevant data, and statistics and allocation of

2   alpha is a very important guideline as you're making

3   that assessment.

4   Defining what your primary endpoints are

5   going to be, how they're going to be analyzed, how

6   you're going to allocate alpha is all very important

7   because statistics can provide a very important guide

8   for whether or not we've hit our standard for strength

9   of evidence.

10   But the ultimate assessment has to view

11   this as a guide and go beyond that, heavily influenced

12   by   that   guide,   but   bringing   in   all   relevant

13   information. If we didn't do that, we wouldn't need

14   advisory   committees   with   multi-disciplinary

15   representation.   We'd   only   need   a   statistical

16   guideline.

17   So judgment has to be brought in, and to

18   answer your earlier question about this composite

19   primary and survival secondary, I would argue that

20   prudence would say you should allocate some alpha to

21   that survival secondary endpoint, and the reason, even

22   though I view that statistics is just a guide here, is

1   ideally I would argue you should choose your primary

2   endpoint on the hierarchy of endpoints as that that's

3   most clinically relevant to a patient, and often

4   that's mortality.

5   But if you really believe that this

6   treatment is not going to positively or adversely

7   affect mortality, it's very reasonable to choose other

8   composite endpoints.

9   If you decide to choose and allocate all

10   of your alpha to that primary endpoint, does that mean

11   you can't look at mortality? I don't believe that's

12   true because mortality isn't just another data driven

13   endpoint. Mortality has always been and likely always

14   will remain an endpoint of particularly profound

15   relevance.

16   DR. MOYE: A surrogate endpoint just the

17   same, of course.

18   (Laughter.)

19   DR. FLEMING: And so if that endpoint

20   shows something that is different than the primary

21   endpoint, should that be factored in? I believe

22   absolutely.

1   Does that violate your alpha? Not

2   necessarily because I factor it in in cases where the

3   primary is positive and the mortality isn't just as

4   much as I do when the primary isn't positive and

5   mortality is.

6   So, in other words, I've been in settings

7   on monitoring boards and on advisory committees where

8   we hit the primary endpoint, but mortality looked

9   unfavorable. Do we approve? Do we stop early? No,

10   we don't. So we're not using all of our alpha then,

11   are we?

12   And as a result, just to finish this

13   thought, if we don't hit the primary, but we get

14   something profound on mortality, I view that, yes,

15   there is room to consider that those data could be

16   convincing. However, you pay a price. You pay a

17   price because I believe that when you have not hit

18   your primary and mortality, which is a very, very

19   important nonprimary measure, is hit, you're going to

20   have to hit it with much more convincing evidence than

21   had you allocated some alpha.

22   So, for example, for example, if you put

1   .05 on your composite, you're probably going to have

2   to hit mortality -- I'm just throwing a number out --

3   at .001, whereas if you had spent .04 on the primary

4   and .01 on mortality, you would have a much easier

5   chance to hit mortality.

6   So I believe even though in my view there

7   are possible settings in which you could hit on a

8   secondary endpoint to which you didn't allocate alpha,

9   you have made the hurdle far higher, and if you really

10   think mortality is a measure that's likely to be

11   impacted in the scenario you created, I would allocate

12   some alpha to mortality.

13   CHAIRPERSON PACKER: I think, Tom, what

14   you're saying, you've actually directly addressed the

15   question that I asked, which is that the passive

16   allocation of alpha, that is, the allocation of alpha

17   to mortality, that is not prespecified, but is implied

18   because of its ultimate clinical relevance does not

19   necessarily protect the sponsor's interest because the

20   level of evidence that would be required for passive

21   allocation, the non-prespecified, clinically driven

22   allocation of alpha, the sponsor would have been, in

1   fact, better of designating their a priori slice of

2   the alpha than to have done it passively, which the

3   level of evidence would have to be far more

4   persuasive.

5   And, Lem, my sense is you do not disagree

6   with that.

7   DR. MOYE: That's right. If by "passive"

8   you mean post hoc --

9   CHAIRPERSON PACKER: Passive is --

10   DR. MOYE: -- is that what you mean by

11   "passive"?

12   CHAIRPERSON PACKER: Passive is non-

13   prespecified.

14   DR. MOYE: Okay. Then I agree with what

15   you said.

16   CHAIRPERSON PACKER: That's correct. A

17   bad term perhaps, but the concept is identical.

18   DR. MOYE: Right.

19   CHAIRPERSON PACKER: Rob.

20   DR. CALIFF: I mean, my interpretation of

21   the strategy that you described is not to try to sneak

22   in the mortality claim when the primary endpoint goes

1   the wrong way, but more to say you think the

2   probability of hitting the combined endpoint is

3   greater, and if you hit that and you show a reduction

4   in mortality, then you're in really good shape.

5   So rather than do it the other way around,

6   where you've worried about the alpha sensitive person

7   and you don't make the mortality endpoint, but you

8   make the combined, then you're in trouble if you have

9   an overly rigid interpretation being made.

10   CHAIRPERSON PACKER: Ray?

11   DR. LIPICKY: I just want to ask Tom a

12   quick question. You mentioned some specific values,

13   P values, that would convince you, so to speak, and

14   for the nonspecified look at mortality, you happened

15   to mention .001, and that would convince you.

16   Why didn't you choose ten to the minus

17   thirteenth? I mean, what is it that got you to .001?

18   DR. FLEMING: I think I said when I threw

19   that out that I'm throwing out something that gives a

20   very general sense. It's a difficult issue to answer,

21   and essentially in my view we are in a position to be

22   guided by these statistical criteria, and these

1   criteria should be preserving the false positive error

2   rate, which is .025, and --

3   DR. LIPICKY: Well, but where does that

4   come from?

5   DR. FLEMING: Where does that come from?

6   That comes from tradition. That comes from

7   essentially the tradition that has been established

8   for strength of evidence for a single trial. I'm

9   talking about a single trial --

10   DR. LIPICKY: Right.

11   DR. FLEMING: -- to be viewed as

12   positive; that whether we use a one-sided .025 or a

13   two-sided .05, they share the same property. The

14   false positive error rate is two and a half percent.

15   DR. LIPICKY: So your expectation that

16   those levels of strength of evidence would be that the

17   trial should be repeated.

18   DR. FLEMING: Well, if you believe that

19   the global strength of evidence required for an

20   approval requires two adequate and well controlled

21   studies, each of which are positive at that single

22   study strength of evidence of .025, then you would

1   need two such studies.

2   DR. LIPICKY: Okay.

3   DR. FLEMING: Obviously there's a lot of

4   discussion ongoing, as you know better than I do --

5   DR. LIPICKY: I understand.

6   DR. FLEMING: -- about whether we need two

7   studies or one study or what is the standard for

8   strength of evidence.

9   DR. LIPICKY: Right. I just wanted to get

10 a feeling for how -- I know the numbers were off the

11 top, and --

12   DR. FLEMING: So I was throwing out a

13 number that was 25-fold smaller --

14   DR. LIPICKY: Right.

15   DR. FLEMING: -- as off the top of my head,

16 and if this weren't mortality, I would throw out a

17 number smaller still, but mortality is a very

18 different and special type of endpoint, and again, I'm

19 comfortable with that because it's readily possible

20 that when you hit the primary and mortality is

21 unfavorable, that that recovers some of the alpha, and

22 as I say, I've had a number of experiences where we

1   haven't viewed positively a result that hit the

2   primary because mortality was unfavorable.

3   DR. CALIFF: Can we address that? I mean,

4   I think as we look more closely in a variety of

5   circumstances that involve patients with heart

6   failure, we're going to see composite endpoints that

7   go in the right direction and mortality trending the

8   wrong direction.

9   There's one coming up next week in Devices

10   actually, which is going to be very interesting to see

11   how it's handled. How do we put that in perspective

12   and deal with it?

13   DR. FLEMING: And what I was referring to,

14   Rob, in my example was a setting where mortality -- we

15   profoundly hit the primary endpoint, but mortality was

16   increased by 40 percent. So a clear-cut example of

17   where net gain was not there.

18   In a setting where you hit your primary

19   endpoint and there is a small trend against mortality,

20   but by no means in any way conclusive, and other

21   secondary measures and safety parameters are

22   favorable, I'm inclined to expect that globally that

1   could still be an approval. I'm not suggesting any

2   time that you have numerically more deaths in the

3   intervention arm than the control arm that that's a

4   nonapprovable agent. I was referring rather to the

5   fact that you can hit a primary and have a

6   sufficiently unfavorable effect on mortality that you

7   would view the data to no longer be convincingly

8   positive.

9   DR. LIPICKY: That really isn't a

10   statistical question, right? I mean that's a value

11   judgment question.

12   DR. FISHER: But it is partly statistical.

13   I mean, number one, it depends on how strong the trend

14   is. When I write papers, I tell my co-authors they're

15   allowed to call a trend if the P value is greater than

16   .05 and less than .1. Otherwise we should just really

17   -- a very low key thing.

18   So I don't know what the strength of this

19   trend is. You probably have a very wide confidence

20   interval typically, and you also have to take this

21   theoretical down side versus what's hopefully a

22   demonstrated up side and evaluate somehow what you

1   think is going to happen to the risk-benefit ratio.

2   I mean if the device is doing really

3   wonderful things in some sense and there's a very

4   small number of deaths, although maybe the relative

5   risk looks bad, but you think it's a small absolute

6   number, I mean, all of these things have to be taken

7   into account.

8   DR. LIPICKY: But you can't offer strength

9   of evidence for the risk-benefit judgment to be made.

10   I mean, how do you do that?

11   DR. CALIFF: Well, can't you construct a

12   probability that -- I hate to sound Bayesian here --

13   but at least in some sense the probability that by

14   looking at the confidence intervals or something, that

15   mortality is within a certain range?

16   DR. LIPICKY: Well, they can do that, but

17   you still have to make the value judgment, right?

18   DR. CALIFF: But that's always true.

19   DR. LIPICKY: If you're willing to accept

20   a threefold increase in mortality, then you accept a

21   threefold increase in mortality.

22   DR. CALIFF: Right.

1   DR. LIPICKY: If you're only willing to

2 accept a 20 percent increase in mortality and the 95

3 percent confidence limit says it can be 300, you would

4 say no. That would be your value judgment.

5   DR. CALIFF: I guess what I hear, I'm

6 worried a little bit about what you said, Lloyd, that

7 if you study few enough patients who die, that the P

8 value is greater than .10 for mortality, that you

9 should just disregard even a threefold increase.

10   DR. FISHER: No, I didn't say that. I was

11 bringing it up because you said a trend, and I had no

12 idea what you meant by that. You know, you might have

13 had one death, you know, in the device group and zero

14 in the control, and 10,000 patients were studied for

15 all I know.

16   Well, that's an estimated infinite

17 relative risk, but if there was tremendous gain within

18 these 10,000, then I would suggest you say that there

19 might be a slight increase in mortality. The event

20 rate is very low.

21   On the other hand, if there were a large

22 number of deaths -- so, I mean, I would need more

1   information before I could deliver a judgment, and

2   this is, I think, what Ray meant when he said it's not

3   a statistical problem, and to me it's certainly not

4   purely a statistical problem, but statistics does

5   enter into it.

6   CHAIRPERSON PACKER: I still haven't heard

7   anyone actually directly address the issue that Ray

8   brought up. Just suppose you have a clinical trial

9   with a drug, and this gets, I think, to the heart of

10   what Rob and Tom -- I think you were trying to get by

11   the, quote, recovery of alpha, which we'll try not to

12   have you explain.

13   But if you had a drug that made people

14   feel better, let's just say it was unequivocal and

15   persuasive, and that 80 percent of the people who got

16   the drug felt better versus ten percent on placebo,

17   and let's just say there was just no doubt about it.

18   And let's assume that, for example, the

19   sponsor evaluated a low risk patient population, and

20   at the end of the assessment there were eight deaths

21   in active treatment group and two on placebo or eight

22   and one. Make any ratio you want, but keep the

1   numbers small so that the data can be misleading. So

2   eight and one if you want.

3   Now, if you do symptom free survival, that

4   doesn't deal with the issue because so many more

5   people are getting relief of symptoms than having

6   events.

7   Eight to one might get people's attention

8   and may or may not reach nominal levels of

9   significance, but would cause people's eyebrows to go

10   up a little bit.

11   How do you deal with that? Because I

12   mean, you can make the eight to one anything you want,

13   but what I'm talking about is a nondefinitive, but

14   worrisome difference.

15   DR. LIPICKY: But I would assert that that

16   is not a statistical problem.

17   CHAIRPERSON PACKER: That's right. It's

18   not.

19   DR. LIPICKY: That is a value judgment

20   problem.

21   CHAIRPERSON PACKER: Right, but you can't

22   recover alpha to solve that problem.

1   DR. FLEMING: I don't want to get

2   sidetracked on recovering alpha. This is a separate

3   issue. The recovering alpha came up in the example I

4   gave where you had 40 percent excess deaths when

5   deaths occurred as frequently as your primary

6   endpoint.

7   CHAIRPERSON PACKER: I see. Okay, fine.

8   DR. FLEMING: So this is a separate issue,

9   and I don't know if Lloyd or Bob has a comment about

10   it.

11   DR. FISHER: I think the problem you're

12   addressing is a really important generic issue for the

13   FDA. I personally have seen it five or six times

14   actually during the past year, and what's harder is

15   not so much eight to one, but it's six to four.

16   So you can look at it one way and say,

17   "Ah-ha, it looks like we have a 50 percent increase."

18   You look at it the other way and you say, "We just

19   switch one number and things are equal."

20   Given the sample size, it could readily be

21   -- but, you know, if it were 50 percent, it would be

22   important. I mean, you know, what do you do?

1   CHAIRPERSON PACKER: What do you do, Bob?

2   DR. TEMPLE: Well, it depends a little.

3   I mean if this were just a symptomatic treatment and

4   you didn't even expect it to alter the natural

5   history, six to four is one of the most likely

6   distributions in either direction you're going to

7   have. It doesn't mean a thing.

8   Eight to one gets more interesting, and

9   the fortunate thing is that doesn't happen that often

10 because if it did you'd be nervous.

11   But you know, you do large numbers of

12 trials and every once in a while bad events are going

13 to go eight to one the wrong way. So that's a very

14 hard problem.

15   We'd probably say you have to do more.

16 You have to study it further, and we'd have our hearts

17 in our throats, and we'd feel bad about it, but we

18 wouldn't know what else to do.

19   DR. LIPICKY: Right. At the last meeting,

20 I believe, that everyone finally said that if you know

21 for sure people feel better, it's okay to have some

22 small risk of excess mortality.

1   CHAIRPERSON PACKER: But you've also

2   reminded us that you don't know if it's small until

3   you study it.

4   DR. LIPICKY: Well, that's a correct

5   statement.

6   CHAIRPERSON PACKER: And that's where the

7   dilemma is.

8   DR. LIPICKY: But, you know, this would

9   take hours and hours, but life is uncertain, and

10 there's a certain element of uncertainty that one has

11 to, I think, accept even at the end of a complete drug

12 development program.

13   DR. DiMARCO: It's also a question of

14 relative risk and absolute risk. If that eight to one

15 is in a 100,000 patient trial, that's not too bad. If

16 it's in a 100 patient trial, it's pretty bad.

17   DR. TEMPLE: That's true.

18   DR. FISHER: But if it's OTC for headache,

19 it might be bad.

20   DR. LIPICKY: So it might be a statistical

21 issue.

22   DR. TEMPLE: You'll never know.

1   CHAIRPERSON PACKER: Bob.

2   DR. TEMPLE: Actually I wanted to go back

3   to another question that Ray asked before, which is

4   the .001 for mortality. I just want to throw

5   something out, and you can all tell me it's whacko.

6   I would argue that it may be that in any

7   trial where you're testing that .05, you might want to

8   say I want to reserve .001 for mortality just in case.

9   So you'd really be testing, assuming appropriate

10   adjustments at .049 over time, which is so close to

11   .05 it doesn't really matter, and you'd be explicitly

12   reserving a little piece for a winner on mortality

13   because that's sort of what we do anyway.

14   Is that a reasonable way to think about

15   it?

16   DR. DeMETS: We actually did that

17   simulation. One, just saying suppose you had .05.

18   How much could you inflate Type 1 error by some

19   criterion? Not much is the answer.

20   So the other thing that we do, the other

21   reserves is .048 or .047, .045, whatever you want, and

22   leave a little bit for mortality. You can also do

1   that in certain conditions, that is, if conditions --

2   if you fail in the primary, which is the only time you

3   really push hard for this anyway probably; you fail in

4   your primary. You go to the secondary. You go to

5   death. You can do that and things come out.

6   DR. TEMPLE: Well, it might be that when

7   one designed a trial with a combined endpoint,

8   something like that, one would say, "Oh, and by the

9   way, I'm reserving .01 for the mortality winner. I

10   don't expect it, but you never know."

11   DR. FLEMING: I would accept that. The

12   worst case scenario is .051, and I'm arguing based on

13   what I was saying before it probably still isn't .051.

14   It's probably still .05 because there are situations

15   that go in the reverse direction.

16   But to follow up on Milt's earlier example

17   though, as a result, you're paying a price. Yes,

18   mortality is on the board. You can use it at .001,

19   but you could have used it at .01 if you had allocated

20   some alpha to it in your alpha spending.

21   And so if you really expect that this is

22   an important measure that truly could be sensitive to

treatment effect, and obviously it would be highly

clinically relevant, you're prudent to not have to

rely on getting a .001.

Getting an .001 on mortality is not easy

in a study where mortality events are not common

because you have to have an observed relative risk

that's really striking, and if you could have gotten

by with only a .01 hurdle, you'd have been far better

off.

DR. FISHER: I would just mention one

slight technical thing. The probability of it being

between .049 and .05 is not .001. It is under the

null hypothesis, but you think you have something that

works, and you shift over and it's greater than that,

and it would be interesting to see, but it's not

phenomenally rare actually that things just sneak

under the line.

I mean I don't know how often I've seen

that in my career, but a number of times, and when

that happens to you --

DR. CALIFF: I think that's a really

important observation because if you have a treatment

1   that probably does work, you're operating in a range

2   where there's a pretty good chance you're going to be

3   right about there if you size your study right.

4   DR. TEMPLE: But the fact is we don't

5   distinguish between .049 and .050 and .051. We call

6   them all the same thing.

7   DR. FISHER: Well, you may not, but Dr.

8   Moye does at least sometimes, and I've seen this

9   committee do things like that.

10   (Laughter.)

11   DR. TEMPLE: And besides, if you do some

12   slightly different analysis, you can make it go either

13   way.

14   DR. FISHER: Pardon me, Lem, if I'm off

15   base. Correct me.

16   CHAIRPERSON PACKER: Let me just make sure

17   that I understand the full implications.   If we

18   reserve .01 or .001 alpha for mortality in a trial in

19   which the primary endpoint is symptoms, and let's say

20   it's done for six months, and let's assume it's not a

21   Class 4 patient population; I just want to make sure

22   that I understand.

1   If one were to do that and assign .001,

2   just you know, let's say every protocol from now on

3   just routinely assigns .001 alpha just so that when

4   you hit mortality you'll get credit for mortality; to

5   me it sounds a little Mickey Mouse because you might

6   actually hit that once in a blue moon, but the number

7   of events is going to be very small.

8   DR. FISHER: Could I make a crazier

9   suggestion than Bob's? If we want to do this, let's

10   change our significance level to, say, .0501 routinely

11   and say the .0001 has to be allocated to mortality.

12   After all, the .05 is extremely arbitrary

13   anyway.

14   DR. CALIFF: I mean, also I just want to

15   register my clinician's concern here. I mean, my

16   relatively lay interpretation of .001, Tom, is that

17   that means and, Lem, is that that means that basically

18   there's less than a one in 1,000 chance that a result

19   at that level or something more extreme could have

20   occurred by chance alone.

21   DR. FLEMING: If this were the only

22   analysis being done.

1   DR. CALIFF: If this were the only

2   analysis being done, and we're in a little bit of

3   Never Never Land, but, you know, at some point you

4   have to ask the question: when am I going to ask the

5   next patient to take placebo?

6   And somehow it's just hard to accept that

7   this is a purely mathematical issue.

8   DR. TEMPLE: That's a slightly rigorous

9   way of saying what you're saying in the first place.

10   What it says is death is always interesting if there's

11   an extreme result, and this is just nominally taking

12   care of building it into the analysis.

13   DR. CALIFF: But I --

14   DR. TEMPLE: It actually does nothing to

15   the analysis to speak of.

16   DR. CALIFF: I guess I'm saying that a .01

17   for mortality, even if it wasn't looked for, to me

18   would be pretty --

19   DR. DeMETS: I mean the numbers are being

20   thrown out off the top of the head. We can get much

21   more exact about what it would take and be much more

22   precise doing things through simulation, but more

1 importantly is the idea, the concept.

2   DR. CALIFF: Okay.

3   CHAIRPERSON PACKER: Ray?

4   DR. LIPICKY: Nothing.

5   CHAIRPERSON PACKER: Okay. Let me suggest

6 that we try to bring this discussion towards a close,

7 and in doing that, let me just summarize a few final

8 comments.

9   There is nothing, I think, particularly

10 controversial around in Section No. 6, which is

11 safety, which we will not be discussing in detail

12 today.

13   Section 7 contains specific and general

14 principles about approvable indications. Let me state

15 that although we were going to spend some time today

16 on that, clearly we don't have the time to do that,

17 but you will notice that the approvable indications

18 are now focused on the patient populations described

19 earlier in the guidelines, that is, the hospitalized

20 patients with symptoms at rest, the ambulatory

21 patients with symptoms on effort, and the ambulatory

22 patients with no symptoms.

1   And in each one of those patient cohorts,

2   one can either give the treatment short or long term.

3   The route of administration may be oral or

4   intravenous, and the therapeutic goal may be symptoms

5   or outcomes.

6   And the purpose, the document takes the

7   position that you can have short or long term goals in

8   the hospitalized patient, which you clearly can have,

9   and your development program should, in fact, be

10   tailored to whether you are requesting a short or a

11   long term indication, and that could be achieved

12   for -- if you want a long term indication, that could

13   be done for an intravenous drug as well as for an oral

14   drug.

15   Section 7.2.1 summarizes the overall

16   guidelines for approval for short term use for

17   hospitalized patients, and I don't think anyone will

18   find anything unusual in that.   That's pretty

19   consistent with all discussions that have taken place

20   to date and, I think, does not require any specific

21   comment.

22   And the same applies to 7.3.

1   DR. MASSIE: I think the one point that

2   might deserve comment is the number of patients

3   exposed.

4   CHAIRPERSON PACKER: Yes. I wanted to get

5   to that in one second.

6   The same thing applies to 7.3 and 7.4.

7   Let me say one thing about what all of

8   these have in common. Each of them has a statement or

9   a paragraph that "the benefits of treatment should be

10   demonstrated   in   the   persuasive   fashion.   This

11   generally requires the benefit be demonstrated in at

12   least two adequate and well controlled trials in which

13   a favorable effect is shown at conventional levels of

14   significance.   Alternatively, if the nature of the

15   benefit is of critical importance to the patient, for

16   example, a reduction in major events, demonstration of

17   benefit in one trial may be adequate for approval if

18   the evidence is persuasive. This generally means that

19   (1) the level of significance in the one trial is

20   comparable to that that would be achieved in two

21   trials with similar findings; that the data within the

22   trial are reasonably complete and of high quality; and

1   (3) that the results are internally consistent and the

2   effects of the drug are still evidence when the data

3   are subject to alternate but appropriate approaches to

4   analysis."

5   All of this is simply to say that the data

6   needs to be robust. They need to be persuasive. They

7   need to be internally consistent, and that if one is

8   going to look at one trial, that the level of

9   persuasiveness would need to be comparable to that

10   would normally be achieved at nominal levels,

11   conventional levels of significance if one had two

12   trials.

13   And this is consistent with all of the

14   decisions and discussions that have taken place in the

15   Advisory Committee for the last several years.

16   The number of patients that are specified

17   in each of these sections is arbitrary and has not

18   been subject to extensive discussion and should not be

19   viewed as being absolute in any sense, but I think

20   that it would be appropriate to say that the data

21   should be of sufficient size that one can address both

22   the efficacy and safety of a drug and assess the risk

1   to benefit relation.

2   And that might vary according to the

3   severity of the disease and the duration of therapy

4   being proposed.

5   And having said that, there is a feeling

6   among some members of the committee and its

7   consultants that sponsors might be advised to collect

8   data in a larger number of patients than they have

9   conventionally done in the past not so much to address

10   the issue of whether the drug works, but to address

11   issues that have arisen in recent applications,

12   including the possibility of differential effects

13   based on baseline demographs, and also the need to

14   adequately describe the use of the drug in patients

15   getting drugs which would be concomitantly

16   administered, and Rob mentioned earlier the example

17   with mebefrodil. This generally requires a larger

18   patient experience than has been evaluated in the

19   past.

20   The concluding comments are

21   philosophically important. These are guidelines.

22   They are designed at the present time based on the

1   present state of knowledge. These will change

2   certainly, and it is really important to emphasize

3   that the most important characteristic of any

4   application that is likely to be approved is the

5   internal consistency of the data and the degree to

6   which the data are persuasive and, in fact, do not

7   raise additional issues that need to be addressed.

8   And none of that can be described in

9   detail in any guideline document. That's a

10   philosophical point of view that requires

11   interpretation as well as judgment.

12   Rob?

13   DR. CALIFF: At the risk of being like the

14   guy at the end of the psychiatry session who brings up

15   an issue, it seems to me that we ought to have some

16   consideration of whether we're pricing heart failure

17   drug development out of the market.

18   That is, you know, for example, in a

19   related cardiovascular -- in another condition related

20   to cardiovascular disease, I actually was astounded to

21   hear that the FDA advised the company not to study

22   patients with serious cardiovascular disease because

1   patients may die, and it would raise questions, and,

2   therefore, they would have to do larger studies that

3   would prolong the duration for waiting for approval.

4   So if we continue to raise the bar on this

5   panel and other areas of the FDA lower the bar, are we

6   really doing a favor to the public health of

7   cardiovascular patients? Because we may be shifting

8   the investment of therapeutic development away from

9   heart failure into other areas.

10   DR. MASSIE: I'm surprised to hear you say

11   that because you're the one that says that you can't

12   judge about safety in populations without large

13   amounts of exposure.

14   DR. CALIFF: I mean I'm obviously asking

15   the question out of some internal anxiety. I think

16   we're doing the right thing for patients by doing

17   this, but the other side is an ugly and difficult

18   issue that I think we at least should consider.

19   DR. MASSIE: But I guess part of the issue

20   is what type of exposure, and particularly in the

21   acute therapy range where this means multifold

22   increase historically.

1   I think it does serve a purpose, but I

2   think it's mostly open label, compassionate use types

3   of exposure that begin to get you some of the hints

4   that you might find out in post marketing issues

5   later, that you can't expect 1,500 patients actively

6   exposed in placebo controlled trials. That's going to

7   break everybody's back.

8   But, on the other hand, why you finish

9   your placebo controlled trials to keep on exposing

10   people, you know, to your drug versus dobutamine or

11   whatever it may be seems to me to be a valuable

12   exercise where you may be able to get a hint of things

13   like drug interactions that you might not have thought

14   about, and that's not so expensive.

15   CHAIRPERSON PACKER: bob.

16   DR. TEMPLE: There are a lot of things

17   that aren't necessarily expensive. It depends a lot

18   on what you do.

19   I think the suggested 1,000 to 1,400

20   patients for acute use is a very substantial increase

21   compared to the past, but the past was a long time

22   ago. So it might be reasonable and it might not, but

one thing to think about is simplifying even there the

data collection instrument and not asking for so many

things.

I mean I think what you're interested in

there is whether people feel better because you can

show that with a small number of patients. You're

interested in survival effects where we really have

very little information, and that's susceptible to

large, simple methodologies which have never been

applied in that setting, but probably should be.

But I guess I want to echo what Rob says.

All of this guidance has to strike some balance

between asking for more of what you want and not

stifling development, and it's a very hard question,

and I, too, was interested to hear that coming from

Rob who has, I think been pushing in another direction

in previous ones, all very good questions.

DR. CALIFF: Let me clarify. I think my

preferred position is not only more patients and about

a tenth as much data on each patient, as you said,

would solve this problem, but it seems like the amount

of data in the trials that we're involved with is

1   headed in precisely the opposite direction because of

2   continued misunderstanding at some level between --

3   DR. TEMPLE: Well, we need a systematic

4   look at that. We're actually getting more and more.

5   This is not a systematic survey, but we're getting

6   more and more inquiries into do we really need to have

7   to collect all of this stuff in those studies.

8   And I can't tell you how the patterns that

9   exist now arose. We have no policy on this, no

10   written guidance.   It's just reflex, and it's

11   susceptible to change and alteration, and it needs to

12   be done.

13   DR. LIPICKY: But I don't see that the

14   implementation, that is, the studies that would

15   conform with these guidelines, is part of the

16   guidelines, not that the question that's being asked

17   isn't important, but if, in fact, one thinks the

18   things that are in this guideline as content are, in

19   fact, relevant to appropriate development in the area,

20   then to do something less because it would cost less

21   I don't see as being necessarily a service to the

22   community or patients because then drugs that don't

1   work or that are very adverse without anyone knowing

2   them will be on the market. That's doing no one a

3   favor.

4   So   the   question   is: how   could   one

5   implement this set of guidelines in some heuristic

6   plan and cut costs? That's an independent question

7   from the things that are being asked for in the

8   guideline, and I don't think they should be confused.

9   I don't know what the right answer is.

10   DR. FISHER: I think there's tremendous

11   room -- I started saying this a long time ago about

12   NIH trials. There seem to be the belief however you

13   design your protocol, you collect everything on

14   everybody, and that just does not have to be so.

15   I mean, you know, if we want to go for

16   certain biochemical measurements or are looking for

17   certain hormones and you start to imbed it in a large

18   trial, why not take a random sample where you expect

19   relatively small numbers if you have some strong

20   relationship?

21   And   my   guess   is   that   virtually   every

22   sponsor in the audience and the world, for that

1   matter, if the FDA is open to those approaches and,

2   you know, happy to discuss them, would head off that

3   way.

4   DR. TEMPLE: But we are known to be open

5   to them because it comes up in this meeting repeatedly

6   and people have asked us about it, and, you know,

7   there are a lot of trials with more intense sub-

8   studies going on. That's a model that has been used

9   repeatedly.

10   DR. FISHER: But normally they add more

11   intense studies on top of something. I'm talking

12   about here's where we want to start, and we say,

13   "Well, gee, do we really need all of this on every

14   patient?"

15   DR. TEMPLE: All I can say is in a two

16   year study there's nothing written about what you have

17   to collect every week or every month or every six

18   months. That's all discussable and negotiable, and

19   there have been trials in which a single sheet has

20   been the data collection sheet, and we've relied on

21   them.

22   So there really shouldn't be any doubt

1   that this is a discussion point that's suitable.

2   DR. THADANI: Even in a short term study,

3   you don't need Swans on everybody, you know, because

4   it says you do 1,000 patients. Everybody doesn't have

5   to be tubed. You could look at, you know, blood

6   pressure, heart rate, and symptomatic improvement.

7   The patient leaves the hospital better.

8   DR. TEMPLE: And if you need a lot of

9   people for rare events, you don't necessarily have to

10   study everything in all those people to get the more

11   common events. There's a lot of ways to design these

12   things.

13   The other thing, as Ray was saying, we do

14   have to be sure you have everything that you really

15   need, but sometimes it's helpful to look at the past

16   and see how much you regret it.

17   And if you're making a change, it's worth

18   looking at how dissatisfied you are with what you've

19   had up to now and, you know, see how urgent the need

20   for much, much greater data is, and we should do that

21   as we look at this.

22   CHAIRPERSON PACKER: Any final comments?

1   If not --

2   DR. THADANI: You know, one other question

3   comes up.   Sometimes the drugs have study on

4   hemodynamics.   Patients are admitted and say

5   hemodynamics improved, but they're not really sick

6   enough.

7   So I just want to echo that these patients

8   for the short term are really sick patients who need

9   hospitalization, are not admitted for the sake of the

10   studies.

11   Sometimes we say, "Okay. We're going to

12   study 300 patients, and if the hemodynamics go in the

13   right way, the patient improves somewhat, but he was

14   only Class 2 and 3." They really do not apply those

15   data to the patients who are in Class 4 failure.

16   CHAIRPERSON PACKER: Okay. If not, I'd

17   like to thank all of our consultants, all of whom

18   played a real important role in today's meeting.

19   And I thank all of the members of the

20   Advisory Committee, and we are adjourned until

21   tomorrow morning.

1   (Whereupon, at 5:13 p.m., the meeting was

2   adjourned, to reconvene on Friday, October 23, 1998.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: 86TH MEETING

Before: CARDIOVASCULAR AND RENAL DRUGS
ADVISORY COMMITTEE

Date: OCTOBER 22, 1998

Place: BETHESDA, MARYLAND

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.

John Mongoven

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